

Transcript of October 18, 2000 Meeting

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SACRAL NERVE STIMULATION

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FOR THE TREATMENT OF URINARY INCONTINENCE

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HEALTH CARE FINANCING ADMINISTRATION

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Medicare Coverage Advisory Committee

Medical and Surgical Procedures Panel

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October 18, 2000

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Baltimore Convention Center

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Baltimore, Maryland

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Panelists

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Chairperson

Alan M. Garber, MD, PhD

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Vice-Chairperson

4 Michael D. Maves, MD, MBA  
 5 Voting Members  
 Angus M. McBryde, MD, FACS  
 6 H. Logan Holtgrewe, MD, FACS  
 Kenneth P. Brin, MD, PhD  
 7 Les J. Zendle, MD  
 Bruce Sigsbee, MD  
 8  
 Consumer Representative  
 9 Phyllis E. Greenberger, MSW  
 10 Industry Representative  
 Eileen Helzner, M.D.  
 11  
 Non-Voting Guest  
 12 Adrian Oleck, MD  
 13 Director, Coverage and Analysis Group, HCFA  
 Sean R. Tunis, MD, MSc  
 14  
 Executive Secretary  
 15 Constance A. Conrad, RN  
 16  
 17  
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1 P R O C E E D I N G S.

2 MS. CONRAD: Good morning. And welcome,

3 panel chairperson, members, guests and temporary

4 nonvoting members. I am Connie Conrad, executive

5 secretary of the Medical and Surgical Procedures

6 Panel of the Medicare Coverage Advisory Committee.

7 The panel is here today to provide advice

8 an recommendations to the Agency regarding sacral

9 nerve stimulation for the treatment of refractor

10 urinary urge incontinence and refractory frequency

11 syndrome.

12 At the conclusion of today's session,

13 panel members will be asked to vote on a series of

14 questions. The answers to those questions will

15 constitute this panel's recommendation, which will be

16 submitted to the Executive Committee. When the

17 Executive Committee ratifies the recommendation, it

18 will officially transmit that recommendation to HCFA.

19 HCFA will then develop a national coverage policy  
20 within 60 days of receipt of that recommendation.

21 For the purposes of today's panel,  
22 Dr. Adrian Oleck, medical director of the durable  
23 medical equipment regional carrier for Region B  
24 received an appointment, temporary nonvoting member  
25 status. Dr. Oleck's expertise will enhance this

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1 panel's deliberative process.

2 In addition, we welcome Dr. Eileen  
3 Helzner, industry representative to the medical  
4 devices and prosthetics panel, who also received an  
5 appointment to temporary nonvoting status.

6 The following announcement addresses  
7 conflict of address issues associated with this  
8 meeting and is made a part of the record to preclude  
9 even the appearance of impropriety. To determine if  
10 any conflict exists, the Agency reviewed the  
11 submitted agenda and all financial interests reported  
12 by panel participants. The conflict of interest  
13 statute prohibits special government employees from  
14 participating that could affect their or their  
15 employers' financial interests.

16 Les, would you make a brief statement for  
17 me please?

18 DR. ZENDLE: Yes. I wanted to let the  
19 panel know that I actually just discovered last night  
20 that Dr. Sharif Aboseif, who is the director of the  
21 neurology program at Kaiser Permanente Los Angeles,  
22 is participating in an IRB approved registry  
23 sponsored by Medtronic and is currently preparing a  
24 publication on the outcomes of patients who have  
25 undergone sacral nerve implantation.

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1 I have no knowledge of the results, and I  
2 and Kaiser Permanent have no financial interest in  
3 the outcome of the study.

4 MS. CONRAD: Thank you, Les.

5 The Agency has determined that all members  
6 and consultants may participate in the matters before  
7 the panel today. With respect to all other  
8 participants, we ask in the interest of fairness that  
9 all persons making statements or presentations

disclose any current or previous financial involvement with any firm whose product or services they may wish to comment on. Thank you.

Dr. Garber.

DR. GARBER: Welcome, everyone. Today I believe all the panel members have a copy of the questions that were in your blue portfolio. We are going to be looking at sacral nerve stimulation for two indications, refractory urge incontinence and refractory urgency frequency syndrome. I think that we will just proceed to ask Jennifer Doherty to present the questions.

MS. CONRAD: Jennifer?

MS. DOHERTY: Thank you and good morning, panel members. In the last panel meeting, you discussed pelvic floor stimulation and biofeedback.

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Today you will discuss the effectiveness of sacral nerve stimulation. Following the public comment period, Dr. Mitch Burken will more fully address the issues that I am about to talk about right now, and answer any questions that you should have.

As many of you know, urinary incontinence, otherwise known as UI, is a major problem in the United States. It affects approximately 13 million adults each year, and at least half of all nursing home residents. These individuals may experience a loss of self esteem and depression. These types of problems have an overall negative impact on quality of life. Unfortunately, there is a great deal of social stigma attached with incontinence, which is one reason why many sufferers do not seek medical attention for this problem. As a result, UI is both under reported and under diagnosed.

There are several treatment options for individuals affected by UI. Patients usually start with behavioral modifications such as bladder training. If that is ineffective, patients commonly move to pharmacologic treatments. Other options include surgical interventions, such as sacral nerve stimulation, otherwise known as SNS.

The sacral nerves are located near the

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1 sacrum, which is the large bone at the bottom of the  
2 spine. These nerves are important because they help  
3 to control bladder contractions. The sacral nerve  
4 stimulator is a pulse generator about the size of a  
5 pacemaker. It is implanted in the abdominal wall. A  
6 wire lead is then attached to the sacral nerves.  
7 Electric impulses are sent from the generator to the  
8 sacral nerves through the implanted wire. These  
9 impulses cause the nerve to contract, which gives the  
10 patient ability to void. Patients are given a  
11 preliminary test to determine if an implantable  
12 stimulator will be effective.

13 You have had the opportunity to review  
14 literature on sacral nerve stimulation. HCFA  
15 provided the following: Two Blue Cross/Blue Shield  
16 technology assessments, one on sacral nerve  
17 stimulation in urge incontinence, and the second on  
18 sacral nerve stimulation and urgency frequency  
19 syndrome. In addition, articles reflecting both  
20 clinical and nonclinical trials were provided.

21 The panel will review the scientific  
22 evidence, hear public comment and make  
23 recommendations to HCFA about the effectiveness of  
24 sacral nerve stimulation. More specifically, you  
25 will be asked to vote on two questions.

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1 Question number one: Is the scientific  
2 evidence adequate to draw conclusions about the  
3 effectiveness of sacral nerve stimulation in the  
4 Medicare population for the following two  
5 indications: Refractory urinary urge incontinence,  
6 and refractory urgency frequency syndrome.

7 Dr. Burken will later provide definitions  
8 of refractory urge incontinence and urgency frequency  
9 syndrome. In answering the question, please consider  
10 the following points: The adequacy of the study  
11 design; the consistency of results across studies;  
12 their applicability to the Medicare population; and  
13 their generalizability beyond the research setting.  
14 We ask you consider the whole spectrum of information  
15 presented, which includes expert testimony and public  
16 comments.

17 If the evidence is adequate to draw

18 conclusions about sacral nerve stimulation and the  
19 panel votes affirmatively on question one, the panel  
20 will move to question two, which addresses the size  
21 and direction of effectiveness. If the panel votes  
22 negatively on question one, please do not proceed to  
23 the second question.

24 Question two asks: If the evidence is  
25 adequate to draw conclusions, what is the size, if

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1 any, of the overall health effect of sacral nerve  
2 stimulation compared with alternative treatments for  
3 refractory cases? Please note that alternatives are  
4 typically other surgical options.

5 When answering the question, the panel  
6 will be asked to place the size and direction of  
7 effectiveness into one of the following seven  
8 categories: Breakthrough technology, more effective,  
9 as effective but with advantages, as effective and  
10 with no advantages, less effective but with  
11 advantages, less effective and with no advantages, or  
12 not effective.

13 Thank you for your time this morning, and  
14 we look forward to a productive meeting.

15 MS. CONRAD: Thank you, Jennifer.

16 Let's proceed with the public  
17 presentations. The first speaker on the list is John  
18 Brizzolara, followed by Jeffrey Welgoss.

19 DR. BRIZZOLARA: Good morning, panel  
20 members. I want to thank the committee for giving me  
21 the opportunity to speak with you about my experience  
22 with sacral nerve stimulation. I think you may have  
23 some data there, I'm going to speak to that data, and  
24 my presentation at the end, I think, will answer most  
25 of the four questions that we will be addressing

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1 today, if not directly, indirectly.

2 As I said, my name is John Brizzolara.  
3 I'm a private practice urologist in Little Rock,  
4 Arkansas. My practice is a general urology practice  
5 with a heavy emphasis on urinary incontinence and  
6 pelvic floor dysfunction or urgency frequency and  
7 pelvic pain. To give you a little bit of background  
8 data on the practice, the population, or the medical

9 draw area of Little Rock is approximately 550,000  
10 people. I am in a 12 member urology group. We see a  
11 large Medicare population; Arkansas is a large  
12 Medicare state. Looking at billing records over the  
13 last several years, it will range anywhere from 55 to  
14 65 percent Medicare billing, so we do take care of a  
15 large Medicare population.

16 I would like to address my experience with  
17 sacral nerve stimulation. I began implanting in  
18 March of 1999 after an excellent training course.  
19 Since that time I have implanted 52 pulse generators  
20 and of that 52, 19 have been in the Medicare  
21 population. In order to get to the 19 permanent  
22 implants, I started with 30 patients who I felt were  
23 candidates for temporary test stimulation. In order  
24 for a patient to qualify for the temporary test  
25 stimulation, they have to have failed conservative

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1 management, and conservative management generally  
2 encompasses pharmacologic treatment or behavioral  
3 modification, or sometimes intravesical treatment.

4 I had 30 patients that fulfilled that  
5 criteria. They all filled out the required voiding  
6 diaries and after reviewing the diaries, these 30  
7 patients then went on to temporary stimulation, or  
8 test stimulation. Out of that 30, I felt that 70  
9 percent, that 19 of those 30, had better than a 70  
10 percent improvement in one of the treatments that we  
11 were looking for. So these patients then went on to  
12 permanent implantation and I will give you the data  
13 on the permanent implantation of those 19, and this  
14 has been over an 18-month period of time.

15 19 patients total. 11 patients or 57  
16 percent had total resolution of their symptoms. 31  
17 percent or six patients had better than a 50 percent  
18 resolution. One patient had better than 30 percent  
19 improvement, and in that one patient, that 30 percent  
20 was significant; it made a large impact on their  
21 quality of life. And then there was one patient that  
22 for some reason did not achieve the efficacy with the  
23 permanent implant that they did in the test  
24 stimulation; I'm not sure why. But of those 19, most  
25 of them had significantly good results.



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1 Prior to treatment, overall, these  
2 patients were using on an average of four pads per  
3 day and these weren't small pads, these were large  
4 pads. So some people were using eight, some two, but  
5 on average, approximately four. After treatment,  
6 they decreased up to 40 percent, which was  
7 significant. Urge symptoms, pelvic pain, decreased  
8 80 percent overall.

9 30 percent of the patients prior to  
10 treatment were undergoing some type of intravesical  
11 treatment which would require the patient to come  
12 into the office at least one day a week for six weeks  
13 to receive an installation, and sometimes the  
14 patients would do this four and five times a year,  
15 which results in multiple visits to the office and  
16 quite a large expense. After treatment, no patients  
17 were receiving any type of intravesical treatment  
18 requiring them to come to the office.

19 Prior to treatment, all patients were on  
20 some type of pharmacologic treatment. That would be  
21 a combination of anticholinergics, tricyclic  
22 antidepressants, alpha blockers, Valium, pain  
23 medication, and most of it was polypharmacy, a large  
24 expense right there. After treatment, oral  
25 pharmacologic agents were decreased to only 10

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1 percent, a significant decrease.

2 Prior to treatment, and this is very very  
3 important in the Medicare population, prior to  
4 treatment, only 20 percent of these patients could  
5 sleep through the entire night without getting up.  
6 Most these people were getting up an average of four  
7 times a night. If you take the Medicare population  
8 and you do not allow this population to get adequate  
9 sleep and they are getting up four times a night at  
10 intervals of every hour, they begin to suffer from  
11 sleep deprivation, which then results in depression,  
12 the immune system is not up to par, and they  
13 subsequently suffer other medical problems. So this  
14 impacts the Medicare population tremendously if  
15 they're not sleeping well at night. After treatment,  
16 greater than 40 percent of the patients slept all

17 night long and of the ones that did not sleep all  
18 night long, on average they were just getting up two  
19 times at night. So they are all getting at least  
20 four hours of consecutive sleep, which is extremely  
21 important.

22 Quality of life issues, which is probably  
23 the reason that we do most of our treatment, impacts  
24 this population tremendously. This is a population  
25 of patients that, the majority are retired, most of

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1 them have the financial means to go and do what  
2 they'd like to do. If you're suffering from pelvic  
3 floor dysfunction and urinary incontinence, it  
4 significantly impacts your ability to get out and do  
5 what you want to do.

6 Prior to treatment, the majority of these  
7 people could not take a 30-minute car ride. Now in  
8 Little Rock, Arkansas, 30 minutes will probably get  
9 you to the mall, to a church, to a relative's, to a  
10 grocery store. But once you're there, that's going  
11 to give you about five minutes to visit, to worship,  
12 to buy your food and then you have to go find a  
13 bathroom. That's a real problem.

14 After the treatment, and this is amazing,  
15 after the treatment, 81 percent of these people could  
16 take a one-hour car ride, most of them over that. So  
17 this allowed them to get out and do what they want to  
18 do. Otherwise, they're sitting at home depressed,  
19 can't mingle, and it impacts them greatly.

20 In my practice, if we're treating a group  
21 of patients, we will do patient satisfaction surveys.  
22 And I don't know if you all have this data. But in a  
23 private practice, patient satisfaction surveys are  
24 very very important. And so I looked at three  
25 different things, were they satisfied with the

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1 treatment, would they recommend it to a friend or  
2 family, and would they repeat the procedure. And I  
3 did a simple scale, zero to ten, zero being no, ten  
4 being yes, 100 percent I would do it.

5 On whether or not they were satisfied, all  
6 patients were more than 70 percent satisfied, two  
7 patients were 70, seven were 80, three were 90, and

8 six were 100 percent. Whether or not they would  
9 recommend it to a friend or family, all more than 90  
10 percent felt they would, 16 said 100 percent they  
11 would and two said 90 percent they would. Whether or  
12 not they would repeat the procedure I think tells the  
13 story. All of them said, probably 80 percent, yes, I  
14 would repeat it; two said 80, one said 90, and 16  
15 said 10.

16 So in the private practice, in a community  
17 based urology practice, in which there's a large  
18 Medicare population, I think and feel that sacral  
19 nerve stimulation provides a very viable treatment  
20 option for this refractory group of patients that we  
21 really had nothing to do before. It improves their  
22 quality of life, their self image, and their overall  
23 well being.

24 The way I have looked at this is that  
25 prior to sacral nerve stimulation, there was a

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1 puzzle, a jigsaw puzzle on urinary incontinence, and  
2 we had most of the pieces, and there was a defect  
3 right in the center for this huge group of patients  
4 that had refractory urge incontinence or urgency  
5 frequency. Other than disfiguring surgery, which  
6 doesn't work in probably 20 percent of the people, we  
7 had nothing to offer them. And thanks to the work of  
8 Siegel, Schmidt, Vinson, and Hadsuna and Chancellor,  
9 and the people in Europe that have done just an  
10 excellent excellent study, a lot of patients, large  
11 number of data, we finally have something, we have  
12 that other piece of the puzzle to fit in here.

13 And I don't know whether Dr. Holtgrewe or  
14 not will agree with me, but if you look at urology in  
15 the last 15 years, we have probably had three big  
16 events. We have had lithotripsy, we have -- that  
17 have impacted patients' lives. We've had  
18 lithotripsy, we have had the introduction of  
19 intravesical BCG for the treatment of bladder cancer,  
20 which has saved a lot of people's bladders. And then  
21 we have sacral nerve stimulation, and it really fits  
22 up there. It was a good study, it was done well, and  
23 it's going to make a big impact. Thank you.

24 MS. CONRAD: Thank you, Dr. Brizzolara.

25 DR. ZENDLE: A question. You may have

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1 said it and I just don't see it written here, is how  
2 long of a follow-up was this? It says research  
3 period December '99 to January 2000.

4 DR. BRIZZOLARA: Actually, it started  
5 March 1999 is when I first started doing the first  
6 implant. Now the data that you have there, the --

7 DR. ZENDLE: Before and after?

8 DR. BRIZZOLARA: Yeah, before and after,  
9 is three months. The last patient you have there  
10 that was implanted, was three months ago. There have  
11 been a few since then that were not included.

12 DR. ZENDLE: So it's a measurement of  
13 three months?

14 DR. BRIZZOLARA: Right. Yes, sir?

15 DR. SIGSBEE: A couple of questions. I  
16 appreciate you coming here today and presenting this  
17 material. First of all, why would there be a  
18 reconnection in pelvic pain? And the second is your  
19 series obviously is a relatively small series; did  
20 you apply any statistics to your results?

21 DR. BRIZZOLARA: I agree, it's a small  
22 series, it's growing from a -- I'll address the first  
23 question first.

24 The pelvic pain problem that we run into,  
25 I rarely see that in a patient that also doesn't have

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1 urgency frequency. Now, why does the technology  
2 work, we're not too sure. There's multiple theories  
3 about the activation or more or less infantile  
4 pathways that are reactivated because of trauma or  
5 whatever. But if you see a patient that has urgency  
6 frequency and it continues, then I see these people  
7 that develop pelvic pain that seem to then go on to  
8 IC. If you can break it at first, if you can stop  
9 the urgency frequency syndrome early, if you can pick  
10 a patient up one and two and three years after they  
11 have started, then you can usually stop the pelvic  
12 pain. But you rarely see pelvic pain without urgency  
13 frequency, so you're going to get both of those at  
14 the same time. Why you have pelvic pain, I don't  
15 think anybody knows at this stage.

16 My data obviously is a small series  
17 because it just began 18 months ago, and I have been  
18 very selective. My criteria has been at 70 percent  
19 improvement on test stimulation, as opposed to FDA  
20 requirements of 50, so it would be larger if those  
21 were included.

22 My statistical data, there have been no --  
23 there has not been a good statistical analysis done  
24 on this data. Whether or not it's statistically  
25 significant would have to be something for the

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1 statisticians, but from a community base, it  
2 statistically impacts my patients to the good, and  
3 that's where I need to look at it, because I need to  
4 be able to offer a patient when they come into my  
5 office with fairly good assuredness that yes, this is  
6 going to work. That's the advantage. There's  
7 nothing else in medicine that I can think of, no  
8 other treatment, that we can actually test first at a  
9 relatively inexpensive cost, that allows us to with  
10 70 to 80 percent assuredness, that a permanent  
11 surgical procedure is going to take care of that.  
12 Where before, the patient came in and they had  
13 refractory urgency, urge incontinence, the only thing  
14 I had to offer them was an augmentation, cystoplasty  
15 or a cystectomy, which is a large surgical procedure,  
16 with probably only 20 to 30 percent improvement.

17 Maybe I carried on too long.

18 MS. CONRAD: Thank you. I may have missed  
19 it; did you state for the record financial  
20 involvement?

21 DR. BRIZZOLARA: I do not have financial  
22 involvement.

23 MS. CONRAD: Thank you, sir. Jeffrey  
24 Welgoss, followed by Roger Dmochowski.

25 DR. WELGOSS: Thanks. You got it right

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1 the first time before so that's okay, I have no  
2 problems with that.

3 Thank you. It's great to be here to  
4 present some statements on behalf of the American  
5 Urogynecologic Society. I'm Jeff Welgoss, I'm a  
6 practicing urogynecologist in Northern Virginia, and

7 a member of the American Urogynecologic Society. I'm  
8 going to refer to that as AUGS, just so I don't have  
9 to repeat it several times. AUGS is a 21 year old  
10 nonprofit organization with nearly 1,000 members who  
11 have a special interest and/or expertise in the field  
12 of urogynecology and reconstructive pelvic surgery.  
13 Our membership includes gynecologists, urologists and  
14 allied health professionals in academic and clinical  
15 practices. The mission of our society is to promote  
16 research and education in the specialty and to  
17 improve the quality and delivery of health care to  
18 women with pelvic floor disorders. I have no  
19 financial disclosures to report, and on behalf of  
20 AUGS, I'm pleased to provide expert testimony on the  
21 clinical value of sacral nerve stimulation, or  
22 perhaps more accurate, sacral neuromodulation in the  
23 treatment of refractory urinary urge incontinence and  
24 urgency frequency.

25 Personally, I have been using this therapy

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1 for the last two and a half years in private  
2 practice. Urinary incontinence has been estimated to  
3 effect up to or perhaps over 20 million patients,  
4 most of whom are women, with an annual cost  
5 approximation in the neighborhood of \$30 billion.  
6 Urge continence is a condition where an individual is  
7 unable to hold urine in response to the sensation of  
8 urgency. This sensation may be triggered by bladder  
9 volume and environmental stimuli.

10 As far as other definitions, urgency is  
11 characterized as the powerful sensation to void, and  
12 AUGS would agree with the definition of urinary  
13 frequency as greater than seven voids daily. Members  
14 of our society of AUGS were involved in the drafting  
15 of the 1992 and '96 versions of the Agency for Health  
16 Care Policy and Research guidelines, which  
17 recommended that a trial of behavioral interventions  
18 be applied to all appropriate patients with urge  
19 incontinence prior to the use of more invasive  
20 treatment such as drugs and surgery, and we continue  
21 to support these recommendations.

22 Behavioral treatments for urge  
23 incontinence include bladder training and pelvic

24 muscle exercises. Biofeedback and pelvic floor  
25 electrical stimulation can be used as an adjunct to  
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1 pelvic floor muscle exercises to improve the  
2 patient's ability to learn and perform these  
3 techniques.

4 Pharmacologic treatment has also been  
5 successful in treating urge incontinence and  
6 overactive bladder. However, pharmacologic treatment  
7 is not without significant side effects, and has to  
8 be discontinued in some patients due to the side  
9 effects.

10 All these noninvasive modalities, however,  
11 are not effective for all patients suffering from  
12 lower urinary track dysfunction such as urge  
13 incontinence and urgency frequency. In a situation  
14 where first-line behavioral and pharmacologic  
15 therapies fail in obtaining remission, AUGS supports  
16 the use of surgical treatment methods that allow  
17 patients to regain a quality of life.

18 Sacral nerve stimulation is reversible  
19 therapy for treatment of refractory urgency frequency  
20 and urge incontinence, and we support the use of  
21 sacral nerve stimulation for the treatment of  
22 refractory urge incontinence and urgency frequency,  
23 as well as urinary retention in those patients who  
24 have failed behavioral treatment including  
25 biofeedback, pelvic floor electrical stimulation, or

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1 found pharmacologic treatments ineffective or not  
2 tolerable.

3 The therapeutic effects of sacral nerve  
4 stimulation rely on electrical stimulation of the  
5 sacral nerve located in the low region of the spine.  
6 The treatment of urinary incontinence with sacral  
7 nerve stimulation involves stimulation by the  
8 implantable system that you have already heard about,  
9 including a lead, a neurostimulator and a connection  
10 between the two. Prior to implanting the nerve  
11 stimulator, the patient must first demonstrate a  
12 positive response during the test stimulation period.  
13 This consists of a three-to-seven day home  
14 evaluation, with an internal lead and external

stimulator, where the patients complete a voiding diary to assess their symptoms. Results at baseline are compared with results during the test stimulation and we would like our patients to demonstrate at least a 50 percent reduction in the primary symptom to be interested for long-term therapy.

Following the successful test stimulation period and after consultation between the patient and physician, the therapy may proceed with the implanting of the sacral nerve stimulator system. The surgical procedure takes between one and three

hours and is usually performed under general anesthesia.

Now just a little bit about data, some of which you already have. The focus of the TEC assessment is on a single study, Medtronic's Multi-Center Clinical Study, using the Inter-Stim system. The study is designed as a prospective randomized trial, and we would like to add, in the comparison group, patients actually served as their own controls.

Of a total enrollment of 581, 260 patients were eligible for implantation. Some of the highlights, I would just like to highlight again. In patients with urge incontinence, 79 percent of implanted patients experienced a decrease of 50 percent or more in incontinence symptoms. 45 percent of the implanted patients reported they were completely dry. Out of the patients with heavy urinary leakage at baseline, 70 percent had eliminated heavy leaks.

Moving on to urgency frequency, approximately a third of implanted patients reduced their number of voids per day by at least 50 percent. An additional third of patients with a baseline frequency of seven or more voids daily reached normal

voiding frequency. 61 percent increased their volume per void by at least 50 percent, and 82 percent improved their degree of urgency prior to voiding, demonstrated by increased volumes over baseline with the same or reduced degree of frequency.



6 Now these numbers are all very well and  
7 good. I would like to stress, however, these were  
8 patients who were failed by numerous other therapies  
9 prior to sacral nerve stimulation, so we're talking  
10 about a population of patients who have been selected  
11 out to be people who have kind of failed just about  
12 everything else we had to offer them prior to that  
13 point.

14 Following up on that, to further document  
15 the effects of sacral nerve stimulation on voiding  
16 function at six months post-implantation, the  
17 stimulation was temporarily turned off and voiding  
18 diaries again collected. Statistical analysis of the  
19 voiding diaries demonstrated a close return to  
20 baseline symptoms for those patients with urge  
21 incontinence, urgency frequency and retention. So  
22 discontinuation of the stimulation resulted in a  
23 return of this dysfunctional voiding pattern.

24 It indicates that the reduction of  
25 symptoms for urinary voiding dysfunction observed

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1 with sacral nerve stimulation was attributable to the  
2 therapy. In addition, these studies demonstrated  
3 that the effects of sacral nerve stimulation therapy  
4 are reversible and not dissociated with any kind of  
5 deterioration of bladder function.

6 Now that's the largest study. When we  
7 look at the remainder of the data, essentially these  
8 results are consistent with just about every study  
9 that has been expressed, and I include a bibliography  
10 of some of the pertinent literature.

11 Just to kind of flesh this out, put a  
12 little skin on this for you, I'm not going to talk  
13 about necessarily large clinical studies, but I just  
14 want to talk about one patient, and I can give you a  
15 whole bunch of anecdotal stories, but once the yellow  
16 light comes on I'll stop. But I want to just talk  
17 about one patient now who is a patient and now a  
18 friend of mine.

19 Carol is 37 years old, two young kids, had  
20 urgency frequency over the last four to five years.  
21 She had been treated with numerous anticholinergics,  
22 she had been treated with Elmiron, she had been

23 treated with bladder retraining, pelvic floor muscle  
24 exercises, pelvic floor electrical stimulation,  
25 essentially everything that the medical community had  
00028

1 to offer, yet she still had to void every hour. Some  
2 of you I assume have driven in D.C. And know that  
3 driving in D.C. Can sometimes be a challenge.

4 Because of this problem, because she had  
5 to void every hour, Carol stopped going out any time  
6 remotely close to rush hour. She stopped going to  
7 her child's soccer games. She was afraid to drive  
8 down to Richmond, so she became almost a social  
9 outcast from her friends, from her friends at church,  
10 from her children's social activities, and it really  
11 impacted her life as far as how she could perform as  
12 a mother, and this was a 37 year old very vital, very  
13 healthy, very bright woman.

14 After having failed all the medical  
15 therapies, finally was implanted after a test  
16 stimulation period, and now voids approximately every  
17 three hours. She's able to go to her kids soccer  
18 game, she's able to see her church again, she's back.  
19 I've got a letter from her mother, a thank you letter  
20 from her mother in Miami, saying you know, thank you  
21 for removing this dark cloud of bladder problems from  
22 my daughter.

23 So just to flush it out, this is a real  
24 therapy that affects patients' lives. So,  
25 concluding, I want to say that sacral nerve  
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1 stimulation provides patients and their physicians  
2 with another effective treatment option to manage  
3 urge incontinence, urgency frequency and  
4 nonobstructive urinary retention. Sacral nerve  
5 stimulation is notably effective in cases refractory  
6 to or inappropriate for conventional therapy. To  
7 further describe the importance of sacral nerve  
8 stimulation, AUGS would stress that this is a  
9 breakthrough technology and has been proven to be of  
10 significant benefit to many patients with refractory  
11 urgency and urge incontinence who have failed  
12 standard therapies.

13 Patients with these voiding functions

14 found to be refractive to standard therapy should be  
15 evaluated by a physician trained in the diagnosis and  
16 treatment of voiding dysfunction. If it is  
17 determined that these patients are candidates for  
18 sacral nerve stimulation, they should be offered  
19 testing and implantation of sacral nerve stimulation  
20 devices as indicated.

21 The American Urogynecologic Society is  
22 hopeful that a positive coverage policy for this  
23 therapy will help to further research and development  
24 of the therapy by the manufacturing community and  
25 continue providing quality health care options for

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1 Medicare beneficiaries. Thank you for your  
2 attention.

3 DR. ZENDLE: Question. Could you just  
4 clarify that you're speaking on behalf of the  
5 American Urogynecologic Society, who feels that this  
6 is breakthrough technology of proven benefit?

7 DR. WELGOSS: Yes.

8 DR. ZENDLE: So you're speaking on behalf  
9 of them?

10 DR. WELGOSS: I am speaking on behalf of  
11 the American Urogynecologic Society.

12 DR. ZENDLE: And the last thing is, in the  
13 last paragraph you say that AUGS is hopeful for a  
14 positive coverage policy so that it will help to  
15 further research and development of this therapy.  
16 Can you just explain, if it's proven, why you think  
17 there should be more research, or is it something  
18 different?

19 DR. WELGOSS: Well, I think we've got a  
20 fairly valuable body of research already. I think  
21 that ongoing research, not only in urinary urgency,  
22 urinary frequency, is going to be helpful in defining  
23 perhaps better those patients that are going to be  
24 most effectively treated by the therapy.

25 There are also a number of other things.

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1 John alluded to earlier about pelvic pain syndrome  
2 and exactly why this works and some of the stuff,  
3 there are theories but nobody knows for sure. But  
4 we've noticed that patients with pelvic pain

5 disorders, interstitial cystitis, often improve with  
6 their pain in addition to the two issues we're  
7 talking about today. In addition, we found that  
8 patients with colorectal dysfunction have also  
9 improved, patients with constipation and irritable  
10 bowel, patients with fecal incontinence.

11 So, I think the area for further research  
12 may be in different indications and also hopefully  
13 fine tuning those patients who are going to be best  
14 able to benefit from the therapy.

15 DR. ZENDLE: Thank you.

16 DR. TUNIS: I just want to ask one quick  
17 question. I know we have spoken in the context of  
18 other incontinence therapies, and I'm just curious.  
19 In your experience, sir, what's the estimated size of  
20 the subpopulation of patients with urgency, urgency  
21 frequency who have failed all the other levels of  
22 interventions you've discussed, the pharmacologic,  
23 the behavioral, the pelvic floor and the biofeedback?  
24 What pool of patients does that leave, in your  
25 experience?

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1 DR. WELGOSS: I think when you take the 20  
2 million or so Americans that leak urine, this is  
3 obviously comparably a smaller pool. Fortunately,  
4 most patients will respond to pharmacological and  
5 behavioral therapies. I don't know that there's any  
6 real estimate as to exactly how large that pool is.  
7 Now, there are some studies that would suggest that  
8 somewhere 50 and 60 percent of patients are unhappy  
9 with the current incontinence therapy that they are  
10 undergoing. Whether or not those are patients that  
11 are willing to undergo a slightly more involved  
12 surgery, a more invasive procedure rather than  
13 continue to take medication and just being unhappy,  
14 nobody has really defined. But I think there is a  
15 body of patients that are unhappy with the therapies  
16 that they're undergoing, and it's probably not as  
17 large as 50 percent of everybody with urge  
18 incontinence, but it's not as small, I think, as we  
19 think.

20 MS. CONRAD: Thank you. Roger Dmochowski,  
21 followed by George Mamo.

22 DR. DMOCHOWSKI: Good morning, panel. My  
23 name is Roger Dmochowski, and I am presenting the  
24 position statement of the American Urologic  
25 Association on neuromodulation for the management of  
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1 voiding dysfunction. My only relationship with  
2 Medtronic is that of an implanting physician.

3 You have been bombarded with a substantial  
4 amount of information. We have given you a similar  
5 bibliography, I think, to what you may have seen from  
6 several other sources. I would reference our  
7 bibliography in your packet and also have you  
8 correlate that with whatever else you have in your  
9 packet from other sources.

10 There has been much discussion today about  
11 demographics of incontinence and I think part of the  
12 problem that you have to deal with is what we have to  
13 deal with as treating physicians. And I as a  
14 urologist will tell you that the demographics of this  
15 disease are changing. Some of that is due to  
16 improved patient awareness and patient acknowledgment  
17 of better therapies out there. We saw a slide  
18 earlier that said 13 million people have  
19 incontinence, recent studies have estimated 17 to 20  
20 million have incontinence, 80 to 85 percent of those  
21 are actually women. So that's probably a more  
22 realistic number, but please keep in mind that you  
23 may in six months see a slide that tells you it's 25  
24 million, because again, as the respondents to varying  
25 survey analysis increase, the number does go up.

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1 Most importantly and of importance to you  
2 as a Medicare advisory group, are in the female  
3 population over 60, 30 to 35 percent of those  
4 patients actually will experience voiding dysfunction  
5 including incontinence. So that's a very important  
6 point to keep in mind in terms of the overall effect  
7 of, disease effect, disease magnitude of effect in  
8 that population.

9 It's hard -- it was a very interesting  
10 question that Dr. Tunis asked regarding what are the  
11 estimates regarding how many patients actually have  
12 the specific disease that we've been asked to

13 evaluate today, which is refractory urgency  
14 incontinence, patients who either have not tolerated  
15 standard therapies or have failed standard therapies.  
16 I can tell you that there is interesting data out of  
17 the pharmaceutical world that says there are actually  
18 1.5 to 3 million patients actually actively on  
19 pharmaceutical medication for OB, quote-unquote,  
20 overactive bladder, which is urgency frequency and  
21 urge incontinence, as previously defined.

22 There are other data that Medtronic I  
23 believe has on file, regarding estimates that they  
24 have regarding the estimated incident of patients who  
25 may be applicable for implant therapy. So again,

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1 keep in mind from the standpoint of what you need to  
2 in terms of evaluating the overall magnitude of  
3 treatment effect is that again, the numbers are  
4 changing, and they are going up rather than down.

5 I think many of you are familiar with the  
6 actual device and the overall point of therapy, which  
7 is direct stimulation or neuromodulation of the  
8 pelvic arc. We don't really know why this therapy  
9 work. There are some very good animal studies to  
10 suggest some neuroplasticity and downgrading of  
11 reflex activity within the sacral reflex, or arc,  
12 both from the afferent and efferent circumstance.  
13 But if you wanted one unifying pathophysiologic  
14 explanation for why this modality works, we don't  
15 have it yet, but it does work.

16 As has been mentioned, the therapy is  
17 delivered via a low sacral approach, and the best  
18 results are obtained with simultaneous fluoroscopic  
19 implantation. Some investigators also use  
20 electromyography to help implantation effect.

21 As has been alluded, there are two phases,  
22 both a test and a permanent phase. The test phase is  
23 a much shorter phase of three to seven days, where  
24 the patient actually via diary communicates with the  
25 physician of the overall response they had to

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1 therapy.

2 The device is composed of two main  
3 components. One is the lead, which is actually the

4 contact point between the nerve and the system, and  
5 then obviously a generator which is implanted through  
6 a separate incision in a site somewhat distant from  
7 the actual lead implant site. There are other  
8 alternative methods being currently evaluated which  
9 we don't have much data for, with regard to  
10 implantation of devices at alternate areas of the  
11 nerve system for neuromodulation, specifically the  
12 posterior tibial nerve. Much has been done with the  
13 old acupuncture treatments.

14 We will limit our literature analysis to  
15 four basic articles, mainly because of the panel's  
16 requirement that they really consider randomized  
17 control data as the most important decision-making  
18 process. There is a substantial body of secondary  
19 information, what would be considered quote-unquote,  
20 secondary information, which you're well aware of,  
21 but from the standpoint of randomized control trials,  
22 I would like to reference the trials by Bosch and  
23 Schmidt, as well as Hassouna, in 1999 and 2000,  
24 respectively, which really formed the basis of the  
25 FDA application by Medtronic for device approval.

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1 The numbers are fairly dramatic; again,  
2 these are patients who have failed other therapies  
3 and intensive other therapies, and you see numbers in  
4 the order of 60 percent cured, substantially improved  
5 in Bosch's study, and 70 percent in Schmidt's study.  
6 Again, very impressive rates when you consider this  
7 refractory population to other interventions.

8 I think a point the panel must keep in  
9 mind to make a balanced decision regarding this is  
10 that currently there is a device revision rate that's  
11 approximating 30 to 35 percent which you should be  
12 aware of, and that has something to do with the fact  
13 that the technology is still somewhat in evolution in  
14 terms of the best way to implant it and ways to  
15 maintain permanent lead contact with the sacral  
16 reflex arc.

17 As I alluded to, Hassouna's publication in  
18 2000 specifically dealt with urgency and frequency.  
19 The prior two were urge incontinence studies. And  
20 again, when you look at the effect of this treatment

on urgency and frequency, again, you see substantial reduction in both frequency and volume voided, as well as degree of sensation of urgency.

And again, urgency is a very subjective phenomenon which is really best analyzed by analog

scales or subjective assessments; it's very difficult to get a quantitation of that in any objective format.

In a very interesting publication which is not specifically a randomized controlled publication, but one that you should be aware of is one that was recently published by Siegel et al., which demonstrates the effect of this therapy is maintained in the majority of patients at 24 months, which again implies the chronicity of therapy does not impact upon overall response.

I think in making your decision you must consider that we don't have a substantial body of randomized control data to make a decision with, but what is out there is well done data and would certainly be classified as primary in terms of the instructions that you have been given. And as I alluded to, there are other secondary type data, objective well done scientific publications that are not randomized control, but which again, vouch for the efficacy of the therapy as delineated by the randomized control trials.

As I alluded to, the revision rates are something that are the function of the technologic development. I think there will be an expected

decrease with time as device innovations occur and as implanting physicians really get over their learning curve and become much more familiar with the therapy. But most importantly, there are no serious morbidities associated with the implantation of this therapy.

And again, I think it's important to realize that there is a necessary expertise that physicians have for this implantation; it's not something that can be done without a training course and rigorous proctoring for the person to reach, or



12 the implanting physician to become capable of  
13 performing the implant without supervision.

14 Based upon the analysis of the literature,  
15 the American Urologic Association would like to go on  
16 record to you as saying that we believe this is a  
17 level 1 or breakthrough technology. It really does  
18 represent a tremendous step forward for patients who  
19 otherwise had only an option of surgical  
20 intervention.

21 The surgical intervention that was most  
22 commonly used in these patients is bladder  
23 augmentation, which has, if you look at the pooled  
24 data from the literature, again, there's no  
25 randomized control data really to look at bladder

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1 augmentation, but only about 30 to 35 percent of  
2 those patients actually do well on that therapy. So  
3 again, you have a substantial improvement over a  
4 straightforward surgical intervention with this type  
5 of intervention.

6 We believe it does have a high magnitude  
7 of treatment effect for patients who have failed  
8 primary therapies, and those therapies were alluded  
9 to previously by the AUGS presentation. I think it  
10 does have, and we do think from the American Urologic  
11 standpoint, that it has a probable substantive effect  
12 on the Medicare beneficiary population. Thank you.

13 MS. CONRAD: Thank you very much. George  
14 Mamo, and the next speaker will be Kristine Whitmore.

15 DR. MAMO: Good morning. I would like to  
16 thank the panel for allowing me to present today. My  
17 name is George Mamo, and I am a private practice  
18 urologist here in the Baltimore area. I have a  
19 specialized interest in urinary incontinence and  
20 voiding dysfunction, and I have been doing this for  
21 about eight years since I finished my residency here  
22 in Maryland, University of Maryland.

23 I direct the Maryland Bladder Center,  
24 which is located at St. Agnes Hospital just a few  
25 miles from here, and I have been doing this therapy

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1 for about two, two and a half years now. I have  
2 become a very active implanter, I have done about 58

3 or maybe 60 implanted generators since I started  
4 doing this, and I have become a firm believer in this  
5 therapy.

6 My relationship with Medtronic is that I  
7 am a proctor. As you may know, most physicians that  
8 want to do this therapy have to go through an FDA  
9 required process where they go through a two-day  
10 certification course and they have been to be  
11 proctored in all the surgeries when they do them. So  
12 I travel around, and I proctor these physicians. I  
13 am here on my own behalf and on behalf of my patients  
14 who have this terrible problem.

15 I feel strongly about Inter-stim and I  
16 think that has provided us with a very good tool that  
17 we never had before. Most patients have been treated  
18 before with behavioral modification or medication and  
19 other ways of dealing with this problem, but all this  
20 has failed. I know of no more treatment options, and  
21 none that are as effective.

22 I have a brief presentation today on my  
23 experience with geriatric patients. In my practice,  
24 we have a very large geriatric population. This is  
25 the data I just presented just two days ago at the

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1 Mid-Atlantic section of the American Urological  
2 Association, which I would like to also present here.

3 We looked at 34 consecutive patients, all  
4 from a range of 60 to 81, so the mean age was 70, and  
5 all these patients have refractory urge urinary  
6 incontinence. Most of them were female, 82 percent,  
7 and most of them have had this problem for many  
8 years, and the mean number of years for this  
9 condition was about 2.3. They all have gone through  
10 all the traditional treating modalities, including  
11 medication, with anticholinergenic drugs in  
12 particular, 97 percent. 91 percent underwent  
13 behavior modification with pelvic floor exercises,  
14 biofeedback, EMG, change in their voiding habits,  
15 change in dietary habits. 40 percent underwent some  
16 form of nonsurgical intervention such as urethral  
17 violation, bladder hyperdistention, and so on. And  
18 approximately 63 percent have had some kind of  
19 surgery, mainly some form of bladder suspension.

20 They all underwent the usual evaluation  
21 with a history and physical examination, and the  
22 urodynamics testing. They all were evaluated with a  
23 48-hour voiding diary which looked at urge  
24 incontinence episodes, pad usage, and frequency, and  
25 the same was done in follow-up.

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1 Of the 34 patients that underwent  
2 percutaneous nerve stimulation, 14 of those or 41  
3 percent were successful and went on to permanent  
4 implantation. Six were dry and eight were greater  
5 than 50 percent improved.

6 I would like to add here that about ten of  
7 those patients that failed had a problem with lead  
8 migration and the lead moved before we could get an  
9 adequate response, so we don't know if those patients  
10 would have responded, so I would guess that there is  
11 probably a certain percent of those that may have  
12 gone on to permanent implantation, so this 41 percent  
13 may actually be a higher number.

14 Of the 14 patients that went on to  
15 permanent implantation, at about six months  
16 follow-up, three were dry, six had a greater than 50  
17 percent improvement in their symptoms, three failed  
18 and two -- three had less than 50 percent  
19 improvement, and two failed. So our overall success  
20 rate was about 65 percent.

21 We compared voiding diaries before surgery  
22 and after, and if you look at the number of leakage  
23 episodes per day, this went down from 7.93 preop to  
24 3.96. The number of pads used went down from 5.11 to  
25 2.32 pads, and both of these were statistically

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1 significant. The voiding episodes per 24 hours went  
2 from 11.75 to 9.5, and this was not statistically  
3 significant.

4 We asked patients about how they felt  
5 about the therapy. 11 of the 14 were satisfied and  
6 would have the operation again, and 12 would  
7 recommend it to family and friends.

8 We did not experience any major  
9 complications or problems with this. Most patients  
10 did well. None of the patients were explanted, none

11 of the patients developed any infections or chronic  
12 pain. We had two patients that had lower extremity  
13 ipsolateral pain for a few weeks after surgery, that  
14 resolved spontaneously.

15 So, I could like to conclude that sacral  
16 neuromodulation in the geriatric population is  
17 effective, and I feel that it definitely has a role  
18 in these patients. I would also like to add that, in  
19 the geriatric patients in particular, those I think,  
20 if you look at the nursing home admission rate, I  
21 think that urinary incontinence is probably one of  
22 the main causes of nursing home admissions, and I  
23 think if we can make an impact on the management of  
24 these patients, then we could make an impact on the  
25 nursing home population. There is a lot of -- a lot

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1 of these patients don't want to leave home, don't  
2 want to go to nursing home, but because of the  
3 problem with incontinence, they even end up having  
4 to, that creates a major problem for their family  
5 members, whoever supports them at home, and they end  
6 up in a nursing home prematurely. So I think if we  
7 can make an impact on their management of their  
8 incontinence, we can make an impact on the nursing  
9 home admissions and there is a lot of ramifications  
10 to that. I think that's all I have to say. Thank  
11 you.

12 MS. CONRAD: Thank you, Dr. Mamo.

13 DR. MAVES: Let me just ask you, can you  
14 take us through sort of, I guess what I need is a  
15 treatment algorithm, for how patients end up to this,  
16 and sort of what the success are. I think you sort  
17 of mentioned using meds, behavioral modification,  
18 nonsurgical treatments, and surgery, and you gave  
19 some percentages of patients in your experience that  
20 had those. But sort of some rough numbers regarding  
21 success, I guess kind of getting down to what can we  
22 expect as a progression sort of, of patients through  
23 this, and what's their chance of success with each  
24 one of those, in your experience?

25 DR. MAMO: A typical patient that comes to

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1 me with urinary incontinence, after they go through

2 their initial evaluation and testing, I usually try  
3 to do some kind of behavioral modification. I start  
4 with some simple things like getting them on a time  
5 voiding schedule, so they void every hour, every two  
6 hours, as opposed to waiting three hours to go  
7 urinate. I try to change some of the things in their  
8 diet like stopping caffeine or spicy food in a diet,  
9 which can irritate the bladder. I start them on some  
10 keen of pelvic floor strengthening regimen,  
11 biofeedback or EMG or electrical stimulation, or  
12 Kegel exercises.

13 Once they go through that process for a  
14 few weeks, if they have not -- or a few months in  
15 terms of the pelvic floor strengthening, I go on to  
16 medication. I try some form of anticholinergenic  
17 drug, Ditropan or Datril or so on. And it's once  
18 they fail those then, if I feel that the patient is  
19 still having significant symptoms and they are not  
20 happy or content with their problem, or if they've  
21 had side effects with the medication even though they  
22 have responded, I will look at considering this  
23 option.

24 Dr. MAVES: And what's your sense, if you  
25 start out with a hundred patients, how many get

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1 better after sort of conservative management?

2 DR. MAMO: I would say with conservative  
3 management, 28 to 30 percent. With medication, you  
4 add another probably another 30, 40 percent. I would  
5 say there is maybe about 40 percent of patients, 40,  
6 maybe 35, who will not respond to any of those and  
7 have to go on to potentially become Inter-stim  
8 candidates.

9 MS. CONRAD: Thank you, Dr. Mamo.

10 DR. SIGSBEE: Just one more quick  
11 question. About 35 percent do not have a good  
12 response at least as you categorized it here. Do you  
13 have any particular characteristics of that  
14 population? You obviously go through a selection  
15 process. Why do those particular people not have a  
16 good response?

17 THE WITNESS: I don't know if I have a  
18 good answer to that. Part of this, I think there may

19 be a psychological component to this, but I really  
20 don't know why these patients do not respond. I  
21 think there is something physiological or anatomical  
22 that we're aware of that explains that, but I don't  
23 think I have an answer to that.

24 DR. GARBER: Okay. Let me just make a  
25 suggestion to the panel. We have a large number of

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1 speakers this morning and it might be best to hold  
2 your general questions to the end, and I hope that  
3 the speakers will stay here so we will have a chance  
4 to ask all of your questions, because I suspect some  
5 of these questions will be addressed in some of the  
6 other presentations. So I would like to ask you to  
7 limit your questions as much as possible after each  
8 speaker speaks, to points of clarification and so on.  
9 And the general questions, hopefully we can pose at  
10 the end of the public speaking section. Thank you.

11 DR. MAMO: Thank you.

12 MS. CONRAD: Kristine Whitmore, followed  
13 by Nancy Muller.

14 DR. WHITMORE: Good morning, distinguished  
15 panel members. Thank you for giving me the  
16 opportunity to testify here today about this most  
17 important topic. I am a proctor for Medtronic and  
18 have no other disclosures to review, and I am here as  
19 a patient advocate.

20 My name is Kristine Whitmore. I am a  
21 clinical associate professor of urology at MCP  
22 Hanneman University, and director of the pelvic floor  
23 institute at Graduate Hospital in Philadelphia. I  
24 have seen more than 10,000 patients with frequency,  
25 urgency, pelvic pain and/or urge incontinence over

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1 the past 15 years, and have been involved in greater  
2 than 20 clinical and basic science research  
3 protocols. I am also a board member of the  
4 Interstitial Cystitis Association, and I will be  
5 testifying this morning on their behalf.

6 The ICA is a national nonprofit  
7 organization dedicated to improving the lives of  
8 patients who suffer from interstitial cystitis or IC,  
9 all of whom have frequency and urgency. IC is a

10 chronic inflammatory condition of the bladder that  
11 frequently goes undiagnosed with patients seeing more  
12 than five physicians and waiting up to five and more  
13 years for diagnosis.

14 The cause of IC is unknown. Therefore,  
15 there is no cure. Treatment options are minimal and  
16 no one treatment is uniformly effective for everyone.  
17 IC symptoms include bladder pain, urinary urgency,  
18 persistent, and day and nighttime frequencies of up  
19 to 60 times a day, suprapubic or perineal pain and  
20 supra-pressure pressure on bladder filling. Although  
21 the average age of onset is 40, 25 percent of IC  
22 patients are under the age of 30 and 20 percent are  
23 well over the age of 65. Although 90 percent are  
24 women, preliminary studies of men with nonbacterial  
25 prostatitis indicate they may have IC as well.

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1 One million U.S. Citizens have this  
2 condition and an exhaustive plethora of treatments  
3 are usually utilized, conservative in nature, but  
4 they fail to provide symptom relief in more than 35  
5 percent of patients. 17 million Americans have  
6 overactive bladder, and IC is perhaps the most  
7 drastic form of the overactive bladder.

8 I would like to share with you some  
9 preliminary data that I have collected that shows  
10 that sacral nerve stimulation is an efficacious form  
11 of treatment for patients with pelvic floor  
12 dysfunction, inability to contract the muscles,  
13 inability to relax high tone muscle spasm. These  
14 patients all have urge incontinence and/or  
15 interstitial cystitis. May I have the slide?

16 So, our purpose was to evaluate the use of  
17 neuromodulation utilizing the Inter-stim device, in  
18 patients with bladder related symptoms and other  
19 pelvic floor disorders. We implanted 17 patients.  
20 15 were females, the mean age was 60, the mean  
21 follow-up period was 13.4 months, 22 months the  
22 greatest. The primary end point was the patient's  
23 perceptions of symptoms. Old fashioned, zero percent  
24 no improvement, 25 percent mild, 50 percent moderate,  
25 75 percent marked, and 100 percent cured. 15 of the

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1 17 had urge incontinence. All 17 had bladder  
2 overdistension cystoscopic evidence of interstitial  
3 cystitis. 10 had pelvic pain as a significant  
4 symptom on a persistent basis. Two had fecal  
5 incontinence which was due to anal sphincter  
6 incompetence. Five had constipation, and three had  
7 diarrhea.

8 So as we can see, there is quite an  
9 overlap of pelvic floor disorders. Most people don't  
10 have just frequency and urgency; most people have  
11 frequency urgency, pelvic floor dysfunction, and/or  
12 concomitant bowel problems. 16 of the 17 considered  
13 the procedure a success; up to 82 percent of patients  
14 reported at least marked, or 75 percent improvement,  
15 for all of their symptoms, except for those who had  
16 sphincteric incompetency fecal incontinence. There  
17 was an average of 9.3 reprogramming events. After  
18 the implant is implanted, we follow them up  
19 regularly, usually at monthly intervals. The mean  
20 amplitude of a max of 10 was 3.1 volts.

21 In the urge incontinence group, 1 cured,  
22 12 had marked marked improvement, so that we can see  
23 70 percent had a success of 75 percent or more  
24 improvement in symptoms. In the interstitial  
25 cystitis population there is no cure available at

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1 this time, but 82 two percent had marked improvement,  
2 which is significant seeing that 35 percent of IC  
3 patients in general report no persistent relief in  
4 their symptoms with our other modalities of  
5 treatment.

6 Pelvic pain on a persistent basis was  
7 found in 10 patients and again, this is usually due  
8 to pelvic floor muscle dysfunction or a high tone  
9 pelvic floor. 20 percent cured, 50 percent had  
10 greater than 75 percent improvement, so that 70  
11 percent were significantly better in terms of their  
12 pain, which also impacts sexual function. 80 percent  
13 of patients with interstitial cystitis have sexual  
14 dysfunction based on a pain basis. These patients  
15 now are able to have sexual activity again, which  
16 greatly impacts their quality of life.

17 And interestingly, GI results of the five



18 who had constipation, four were markedly improved.  
19 Of the diarrhea patients, two of the three were  
20 markedly improved. And as we mentioned, there were  
21 failures in the sphincteric anal incontinence. The  
22 therapy obviously was not chosen for these people,  
23 this was a concomitant disorder.

24 So you can see a significant reduction in  
25 bowel problems as well as bladder problems. There

00053

1 thus was a significant symptom relief reported by  
2 patients with urge incontinence, interstitial  
3 cystitis, pelvic pain, diarrhea and constipation.  
4 Sacral nerve stimulation continues to be an  
5 efficacious form of treatment for patients with  
6 pelvic floor dysfunction.

7 En route is a multicenter studies on  
8 symptoms improvement with a test stimulation portion  
9 of the procedure in patients with diagnosed IC, and  
10 also follow-up data which will show scientific  
11 evidence that is of statistical quality, will be  
12 delivered on voiding diary, O'Leary symptom, and  
13 problem index for IC, Likert scales for urgency and  
14 pain, a Rosen's sex questionnaire and a bowel diary.

15 IC is a severe form of the overactive  
16 bladder affecting one million Americans. Inter-stim  
17 therapy is a valuable form of therapy for patients  
18 refractory to standard conservative therapy, and may  
19 prevent cystectomy, radical surgery, as the only  
20 therapy left for a group of patients who has failed  
21 all conventional therapies for IC. I would encourage  
22 you to vote yes on this breakthrough technology.

23 I will give you one brief story. Wally is  
24 48 years old. He has been a television talk show  
25 host for 22 years. I met him four years ago, on the

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1 verge of being fired because he was on narcotics,  
2 couldn't focus, he had gained weight, because he had  
3 frequency urgency and severe pelvic floor dysfunction  
4 with pain. He had tried dietary modification,  
5 bladder retraining, physical therapy for his pelvic  
6 floor muscle dysfunction, Elmiron therapy, which is a  
7 drug that is used commonly for Elmiron, and pretty  
8 high level antidepressants and narcotics. He is 2.2

9 years out now. Wally has a television show, he has a  
10 large following, he has no narcotic utilization, he  
11 is off his antidepressants, and he is sexually active  
12 again for the first time in almost 16 years. Thank  
13 you very much.

14 MS. CONRAD: Thank you, Dr. Whitmore.  
15 Nancy Muller, please, followed by Janet Smith. We  
16 do have a cancellation, if you're following. Dave  
17 Gordon is not here today.

18 DR. MULLER: As the executive director of  
19 the National Association for Continence, I am both  
20 honored and pleased to be with such leading  
21 authorities speaking on the value of sacral nerve  
22 stimulation in the treatment of refractory urge and  
23 urge frequency incontinence. My association, by the  
24 way, with Medtronic is that the company is one of  
25 about 18 industry council members contributing to our

00055 organization. I am here today as a patient advocate.

2 First of all, who and what is represented  
3 by the National Association for Continence or NAFC?  
4 We're the single largest, most prolific consumer  
5 advocacy organization devoted exclusively to  
6 incontinence in the world, and I can personally  
7 attest to this because I have represented NAFC at  
8 gatherings such the International Incontinence  
9 Society meeting, as far as away as Athens, and World  
10 Health Organizations on the subject in Bonn.

11 While the mailing list of our quarterly  
12 newsletters reaches initially 130,000 individuals,  
13 we know that the readership is at least a quarter of  
14 a million people, because our literature is so freely  
15 shared by our readers. We are broadly funded by  
16 industry, foundations, health care professionals, and  
17 our consumer members. We have a proactive agenda,  
18 not a work plan driven by the funding of special  
19 interest groups. Since our inception about 20 years  
20 ago, our mission of consumer advocacy, education and  
21 information dissemination through networking, has not  
22 faltered.

23 Well, you know the numbers on  
24 incontinence, you heard them earlier. As many as 25  
25 million Americans suffer from urinary incontinence,

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1 and at least 18 million of those are experiencing  
2 chronic rather than transient incontinence. But how  
3 do these consumers, how do these individuals really  
4 feel? Well according to the research that we have  
5 conducted on our newsletter readership, 20 percent of  
6 survey respondents indicate that their incontinence  
7 is a major problem, and there is no statistical  
8 difference in these responses by gender. Those in  
9 the lowest income bracket are disproportionately more  
10 seriously affected they say, as are those under age  
11 45, because of the quality of life they feel they're  
12 sacrificing. And satisfaction with treatment or  
13 dissatisfaction as the case may be, is not a function  
14 of how much they are spending on managing or trying  
15 to treat their incontinence.

16 We have done now six of these surveys over  
17 the last 20 years, our most recent was completed last  
18 year, and the one before that in 1996. And as you  
19 heard from an earlier speaker, the level of  
20 dissatisfaction with treatment for a variety of  
21 reasons is quite high. It hovers around 62 to 63  
22 percent of the people responding to the survey. This  
23 may partially bespeak the sheer complexity of  
24 properly diagnosing and treating incontinence, but it  
25 also suggests that there are gaps in what people have

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1 access to.

2 Where can consumers turn? Well, sacral  
3 nerve stimulation should be explored as a midline  
4 option, we feel as an organization. Patients seeking  
5 answers may have unsuccessfully enrolled in  
6 everything ranging from pharmacotherapy,  
7 hydrodistension, external stimulation in the form of  
8 transcutaneous biofeedback, urethral dilation, pain  
9 management of different degrees and sorts, cones,  
10 timed voiding, psychological counseling, and even  
11 surgery sometimes. Just imagine, over the years and  
12 years of undergoing this, how frustrated they must  
13 feel.

14 And I hasten to point out that consumers  
15 tell us in the research that we conduct that they  
16 actually prefer conservative therapy. In fact, a

majority of respondents to our more most recent consumer survey indicated that they were most pleased with the behavioral therapies that they had pursued for their incontinence. But, I will add that the ones that are most pleased tend to also be the ones who either suffer from slight leakage or have been diagnosed with stress or stress urge incontinence. The reason I point this out is that sacral nerve stimulation is designed to treat the symptoms of urge

or urge frequency incontinence, not stress incontinence.

And I will add just two more statistics that I think are revealing. Only 3.3 percent of our survey respondents considered themselves cured following what they deemed to be their most helpful treatment, and only 8.6 percent expressed that they were very pleased with their outcomes. Clearly, there's a gap.

Why does urge and urge frequency incontinence affect peoples lives so significantly, why is it so much more debilitating and isolating than stress incontinence? Well, there are a couple of reasons. First of all, it's just downright unpredictable. You have already heard the stories about trying to get through traffic and to children's soccer games, or to attend church. The accidents tend to be larger, in other words, when urine is lost, a larger amount of urine is lost than it typically is with stress incontinence, and absorbent products aren't always enough protection, so there's room for lots of social embarrassment. The frequency of urination tethers the individual to the toilet or to a urinal; it thereby restricts their freedom and their activities.

Those without access to sacral nerve stimulation, who are otherwise valid candidates, face a more drastic and more morbid option, such as urinary diversion, or they simply face remaining incontinent and miserable. Finally, we have a less radical, or less extreme choice.

But who are these people? Just think of

8 them as individuals. They are individuals with  
9 multiple sclerosis or spinal cord lesions, or  
10 neurologic disorders, just to name a few examples.  
11 How much do our country's continence care specialists  
12 believe in sacral nerve stimulation? Well already,  
13 even though this is a relatively new procedure, 120  
14 of NAFC's 750 continence referral affiliates are  
15 fully trained in sacral nerve stimulation. Now, this  
16 database of sources, names that we give to consumers  
17 when they call us asking for help, go through an  
18 elaborate grid of questions by us to qualify them,  
19 and I think it's significant that on that list of  
20 those trained in sacral nerve stimulation include the  
21 likes of Rod Appel at the Cleveland Clinic, Janelle  
22 Foote at Shepard Spinal Cord Injury Center in  
23 Atlanta; both of them are on our board of directors.  
24 Neil Galloway, who's head of the continence center at  
25 Emory, and Alan Wing, the co-chair of the Bladder

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1 Health Council, just to name a few.

2 What we're really talking about here is  
3 quality of living, not life or death scenarios, and  
4 in this day and age, we are living the reality of  
5 chronic illnesses and conditions, not catastrophic  
6 traumas that threaten our existence. And when people  
7 don't have access to answers and they suffer from  
8 retractable urge or urge frequency incontinence, they  
9 have a tendency to do a few things. They restrict  
10 their water or fluids, leading to constipation, which  
11 exacerbates their symptoms. This can lead to also  
12 dehydration or chronic urinary tract infection, all  
13 which need medical intervention. Or they may suffer  
14 from slips and falls when rushing to the toilet and  
15 this can result in broken hips, and fractures,  
16 arthritic conditions, immobility, and again, they are  
17 still saddled with their incontinence.

18 I would like to echo Dr. Brizzolara's  
19 remarks about sleep deprivation and disorientation  
20 and depression, already a major problem in the  
21 elderly. And I echo too Dr. Mamo's remarks regarding  
22 incontinence in nursing home admissions. Research  
23 does show that it's the top two or three reasons that  
24 families and care givers take an individual to a

25 nursing home.

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1 I call this panel to action to recognize  
2 sacral nerve stimulation among the repertoire of  
3 options for individuals, as a medical necessity when  
4 other more conservative treatments fail, and to  
5 return dignity to life, and life to living. Thank  
6 you very much.

7 DR. OLECK: I just have a question. A  
8 number of the physicians have talked about  
9 satisfaction surveys that they have done on their  
10 patients and we know that sometimes patients may feel  
11 pressured in their response to questions from the  
12 physician who did that. I am just wondering whether  
13 your organization does any satisfaction surveys with  
14 respect to various treatments for urinary  
15 incontinence, and if you in particular, whether you  
16 have done any kind of survey with respect to this  
17 procedure?

18 DR. MULLER: Our surveys have just begun  
19 to ask questions about satisfaction with treatment  
20 because in the past our questions focused more on  
21 just how motivated people had been to seek proper  
22 diagnosis and treatment. And we're now, as more and  
23 more are seeking treatment, we are turning our  
24 questions to that. We have not segregated questions  
25 regarding satisfaction in such a way that we could

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1 correlate sacral nerve stimulation treatment with  
2 their responses to their level of satisfaction,  
3 mainly just because the numbers are still too small  
4 to be statistically valid. But we are starting to  
5 compare responses by diagnosis, and that's what I  
6 spoke about a few minutes ago regarding those  
7 satisfied who had been diagnosed with stress, versus  
8 those who had pursued nonbehavioral treatment.

9 DR. OLECK: Thank you.

10 DR. ZENDLE: Do you have focus groups and  
11 groups for patients with incontinence so that if  
12 patients who underwent this were unhappy with it, you  
13 would have heard, or if here they are happy with it,  
14 do you hear, or isn't that really the function or  
15 purpose or role of your organization?

16 DR. MULLER: Generally, we hear when  
17 people are frustrated, those are the people who are  
18 calling us saying they've tried this, they tried  
19 that. We are, because we are a national  
20 organization, it's a little hard to organize focus  
21 groups around the country, because it's a little hard  
22 to get, to solicit people to sit in a room and talk  
23 about their incontinence. We have in the past year  
24 just formed a new consumer advisory panel, so those  
25 are questions that we can begin to ask, but what we

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1 try to do is match up people with resources for  
2 further treatment.

3 We don't know all the reasons for why they  
4 are dissatisfied, we don't know if it's because they  
5 had unrealistic expectations in the first place, we  
6 don't know if it's because they went to a health care  
7 provider who wasn't fully trained in incontinence  
8 diagnosis and treatment, or if they just got  
9 misdiagnosed and therefore, mistreated. So we don't  
10 really don't know all the reasons for why they are  
11 unhappy.

12 MS. CONRAD: Thank you. Janet Smith  
13 please, followed by Kimberly Oleson.

14 DR. SMITH: I'm Dr. Janet Smith. I'm in  
15 solo private practice in Sioux Falls, South Dakota,  
16 and I'm here on behalf of my patients. I have no  
17 interest in Medtronic except that I implant and use  
18 the nerve stimulator myself. I started in February  
19 and so far I've implanted 12 patients, so they are  
20 small in number but the results have been  
21 significant.

22 And if you would have told me seven years  
23 ago when I started doing more pelvic floor  
24 dysfunction that I would be doing these instead of  
25 radical prostatectomies and nephrectomies, as a

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1 surgeon, you know, to treat the patients  
2 conservatively goes against our training basically,  
3 from way back when. And these patients had been the  
4 most satisfying patients I have ever dealt with, and  
5 now with the new Inter-Stim device, I have something  
6 else I have to offer for those patients that do not

7 respond to the conservative treatments.

8 What I'd like to do is just mention a  
9 couple things that haven't been mentioned. As far as  
10 the test stimulation, it's probably at least six  
11 months before my patients are even considered to be  
12 an Inter-stim candidate. I my mention it earlier if  
13 they've been to multiple physicians, if they're  
14 voiding like 30 times a day, or I doubt whether  
15 medical management, conservative management is going  
16 to work, at least I mention it to them to give them  
17 hope, that something can be done if we don't get  
18 resolution of their symptoms.

19 The test stimulation, they need to do a  
20 diary ahead of time. The test stimulation, a lot of  
21 time I'll be there an hour to an hour and a half,  
22 trying to get the temporary lead placements into  
23 maximum position. So it is time consuming and you  
24 have to be patient. If they pass the test  
25 stimulation, which two-thirds of my patients do pass

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1 it, which shows a 50 percent of improvement in their  
2 symptoms, and these patients are so happy when they  
3 come back to get their wires removed that you don't  
4 even have to look at their diary, you know how happy  
5 they are, and it's that dramatic.

6 For the permanent implant it does take  
7 about an hour up to two hours to do the permanent  
8 implant, and then the patients do go home and usually  
9 in seven to ten days, we activate it. So these  
10 patients, because they've been through so much, are  
11 usually patient with the process of getting it in,  
12 plus they've had their test stimulation so they know  
13 how the permanent implant is going to work.

14 And I know some of the speakers talked  
15 about the geriatric population, but a lot of these  
16 patients because of back injuries, some because of  
17 their bladder, are on disability or Medicare as  
18 fairly young patients, so some of my patients are  
19 even in their 20s and 30s on Medicare.

20 You have copies of the letters and I would  
21 just like to go through a couple of them. The first  
22 one is Phyllis, and Phyllis is a diabetic and has  
23 urgency frequency but also was not emptying



24 completely, so her urine was like a sewer for four  
25 years that I knew her. I couldn't get the infections  
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1 cleared. I finally put her on intermittent cathing,  
2 she went on insulin to help control her diabetes, we  
3 diagnosed reflux so she had a bilateral  
4 reimplantation; at the same time I tried to wrap her  
5 bladder to make it empty better. It didn't work.  
6 She couldn't do self cath herself, so her husband did  
7 it twice a day to try to get her bladder empty. Even  
8 though all this was done, she was on antibiotics, I  
9 tried her on Volmax, Hytrin, Urecholine, everything  
10 that I had to offer, her urine was still constantly  
11 infected.

12 She had two test stimulations. The first  
13 one didn't work, and so she was willing to try a  
14 second one, and the second one we did under  
15 fluoroscopy, and it was a matter of two millimeters,  
16 of moving the wire to get a response or not get a  
17 response, so she actually did see an improvement with  
18 the second test stimulation. She has now been  
19 implanted for five months, she is not cathing herself  
20 anymore, her urine has been sterile now for four  
21 months.

22 The next one is Donna. Donna always says  
23 she's my problem child. I did a sling on her that  
24 failed, I did a second sling, this time using bovine  
25 graft, which she eroded, but everything was scarred

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1 in very nicely, but she still had incontinence. So I  
2 did chonigen injections three times, and again, she  
3 had significant urgency, frequency urge incontinence.  
4 With the Inter-stim she is now dry. She can go  
5 camping again without having to find a bathroom every  
6 place or go behind a tree, and she has significant  
7 improvement in her quality of life.

8 Sherry is a 40 year old who has chronic  
9 fatigue syndrome, fibromyalgia, and kidney stones.  
10 We couldn't have her drink much because she was  
11 living in the bathroom, or she wouldn't drink  
12 anything. Nothing we tried worked for here, and  
13 again, she is a successful Inter-stim patient who now  
14 has her life back.

15               Gina is another 40 year old on disability,  
16 has multiple psych medications, and again, we tried  
17 her on all medical management, physical therapy, and  
18 despite that, she was going to the bathroom over 30  
19 times a day. For years, she hadn't gotten any more  
20 than an hour's worth of sleep at one time. And we  
21 did her test stimulation, she came back in the office  
22 a new person. She had actually slept seven hours in  
23 a row, the first time in 20 years. And she's an  
24 artist. She came back with drawings that she had  
25 drawn 15 years ago, and it basically was really

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1       dramatic about how it demonstrated the pelvis and all  
2 the pain and discomfort her pelvis and her bladder  
3 were causing her.

4               She was my very first implant. She didn't  
5 get the success she got with the test stimulation,  
6 and she was willing to undergo another surgical  
7 procedure to readjust the lead placement because she  
8 knew what was possible. And now she is much better  
9 off and in fact, she's riding a bicycle and just fell  
10 off her bicycle.

11              Another patient was a back injury patient  
12 who, my one goal in life was to come into the exam  
13 room and see her sitting down. And when I first  
14 mentioned the Inter-stim to her, she said no way, I  
15 don't want a foreign device in my body. I said well,  
16 just look at the videotape, and she saw the  
17 videotape, I walked into the room, she was crying and  
18 said when can I sign up.

19              She hadn't been able to sit through a  
20 movie, her family was constantly giving her grief  
21 about what she drank, didn't want to travel with her  
22 because they had to stop so much, and with the  
23 Inter-stim, her life has really changed around as  
24 well. She can now sit through a movie without having  
25 to go to the bathroom.

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1              So, this has dramatically increased my  
2 practice. As far as patient satisfaction, I have  
3 something to offer them that I never had before.  
4 It's a breakthrough procedure and there really is  
5 nothing that compares it to that has the outcome that

6 I found. Thank you.

7 MS. CONRAD: Thank you, Dr. Smith. Let's  
8 do one more before we take a break. Kimberly Oleson.

9 DR. OLESON: Good morning. My name is  
10 Kimberly Oleson and I am an employee of Medtronic.  
11 Until July of this year I was the principal clinical  
12 programs manager for the Medtronic functional  
13 stimulation business. Currently I am the director of  
14 clinical operations for Medtronic's E/T systems  
15 business.

16 In collaboration with the global study  
17 investigators, the design of an FDA regulated  
18 multicenter trial began in 1992. The purpose of this  
19 trial was to evaluate the safety and effectiveness of  
20 sacral nerve stimulation therapy for the treatment of  
21 specific voiding disorders. It gives me great  
22 pleasure to provide with you with background  
23 information on this study. It looks like I may be  
24 missing a slide.

25 In terms of background, the genesis of

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1 sacral nerve stimulation therapy was born out of  
2 early work by Schmidt, Tanagho and others at the  
3 University of California San Francisco, in connection  
4 with the NIH neuroprosthesis program. This group  
5 explored the complex innervation of the sacral nerves  
6 as they innervate the pelvic floor and the viscera,  
7 including the bladder. They hypothesized that  
8 stimulation of the sacral nerves would modulate  
9 dysfunctional and organ behavior. They explored this  
10 work in animal and cadaveric models, and trial  
11 stimulation of the sacral nerves in human feasibility  
12 studies was accomplished via percutaneous access  
13 through foramen or existing holes located in the  
14 sacrum to access the sacral nerves.

15 In all cases when we talk about sacral  
16 nerve stimulation, it's important to note that we  
17 mean that this is transforaminal sacral nerve  
18 stimulation therapy. Success with trial stimulation  
19 and early feasibility studies in humans resulted into  
20 the development and the need for more long-term  
21 therapy. Therefore, implantable systems were  
22 developed.

23 Today the Inter-stim system, as seen on  
24 the screen, is comprised of a lead, a  
25 neurostimulator, and an extension that connects those  
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1 two devices. This is the same technology that has  
2 been commercially available in the United States  
3 since the mid 1980s for the indication of spinal cord  
4 stimulation to treat trunk and limb pain.

5 In this presentation, my task is  
6 threefold. First, I will present what is sacral  
7 nerve stimulation; secondly, provide key definitions  
8 used in the clinical study; and third, review the  
9 clinical study design. This presentation is intended  
10 to set the stage for Dr. Steven Siegel as he presents  
11 results from clinical study, and for Dr. Thomas  
12 Benson as he defines more clinical applications of  
13 sacral nerve stimulation therapy.

14 Medtronic had sponsored a multi-center  
15 randomized trial in December of 1993. This trial  
16 involved 22 global investigative sites and the  
17 purpose of this study was to evaluate safety and  
18 effectiveness of SNS therapy for the indications of  
19 urge incontinence, urinary urgency frequency, and  
20 nonobstructive retention. As defined in the study  
21 protocol, urge incontinence is defined as an  
22 involuntary loss of urine associated with the strong  
23 urge or desire to void. Urgency frequency is defined  
24 in the study as an uncontrollable urge to urinate,  
25 resulting in very frequent and small volume voids.

00072  
1 And nonobstructive retention is comprised of partial  
2 retention or complete retention. And in all these  
3 cases, mechanical obstructions have been ruled out  
4 before entry into the trial.

5 SNS therapy is delivered in two different  
6 stages. The first is test stimulation, and the  
7 second is surgical implantation.

8 Test stimulation is a procedure that is  
9 intended to evaluate SNS therapy on a trial basis in  
10 patients before they are considered for surgical  
11 implantation. In this procedure, a needle, a foramen  
12 needle is used to percutaneously access the sacral  
13 nerves, to provide acute stimulation in the

14 physician's office under local anesthetic. Once the  
15 stimulation location is identified, acute stimulation  
16 is applied to the subject, and the physician learns  
17 how to optimize location by looking for very specific  
18 motor and sensory responses to acute stimulation.  
19 Once these locations are you identified, a test  
20 stimulation lead is passed through the cannula of the  
21 needle, percutaneously placed, and the patient is  
22 actually sent home for a trial period of three to  
23 seven days.

24 During this time patients will fill out in  
25 the baseline and test period entries in a diary in an

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1 effort to quantify the effects of stimulation on  
2 their voiding pattern. The data collected at  
3 baseline and during the test stimulation period,  
4 consistent with standard urologic research, only  
5 patients with a 50 percent or greater improvement as  
6 documented in order to consider a subject for a  
7 long-term therapy or surgical implantation.

8 And as advocated by the medical community  
9 and the AHCPR guideline, voiding diaries comprise the  
10 primary outcome parameter in this particular study.  
11 For each of the three indications, we selected key  
12 parameters relevant for that condition in order to  
13 determine success or efficacy of the therapy. For  
14 example, for urge incontinence, we look at the number  
15 of leaking episodes per day, the severity ranking of  
16 those leaks, and those are ranked by patients as  
17 mild, which means drops or urine; moderate, which  
18 means one to two tablespoons of urine leaked; and a  
19 severe leak or heavy leaking, which is defined as  
20 soaking the pad, diaper or patient's outer garments.  
21 And finally, we recorded the absorbent and pad diaper  
22 usage because of leaking episodes in this study.

23 For the indication of urgency frequency,  
24 we looked at frequency of voids, volumes voided, and  
25 the perceived degree of urgency prior to voiding.

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1 And finally, for retention we looked at  
2 catheter volumes in this study.

3 Study enrollment was based on very  
4 specific inclusion and exclusion criteria in this

trial. It is important to note that in this study, as noted in the inclusion side, patients must have demonstrated failure of conservative therapy or conservative therapy was deemed medically inappropriate for that patient before entry. And although the literature may suggest that SNS therapy may be beneficial for other subpopulations or indications, we purposely excluded neurogenic conditions, primary pelvic pain and primary stress incontinence in order to minimize the potential for confounding factors for this particular study.

And here's how the clinical study design worked. Within each of the three indications that we studied, all patients underwent test stimulation. A positive response to test stimulation, meaning a 50 percent or greater reduction in their primary symptoms resulted in randomization in the study to one of two treatment arms. In the first arm, control, the control group patients did not receive SNS therapy; they were allowed to continue standard medical care for a period of six months. The

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standard of care included treatment such as pharmacologics, biofeedback, et cetera. At the end of the six-month waiting period without stimulation, if appropriate, they were allowed to cross over to the treatment arm of the study.

In the treatment arm of this study, subjects were immediately implanted with the SNS system and were followed then post-implant through a period of six months. After the six-month implant visit, subjects returned to the clinician's office and underwent as part of the patient consent what's known as a therapy evaluation test, in that the investigator deactivated the stimulator and over a period of several days documented the voiding diaries that patients filled out to see what happened to their behavior with stimulation off. After returning, if they wished, they may have the device reactivated, and they're followed every six months until the study was terminated.

In this particular design, this randomized design, efficacy was evaluated at three points: Six

22 months, treatment versus control stim on versus no  
23 stimulation; at therapy evaluation, stim on versus  
24 stim off; and then of course on chronic follow-up,  
25 stim on long term versus no stimulation at baseline.

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1 Safety was prospectively documented  
2 throughout the follow-up period. Now, the  
3 investigators were successful in designing a study  
4 protocol that was randomized that could document the  
5 effects of SNS therapy, however, long debated the  
6 issue of incorporating a placebo control. The  
7 investigators, the FDA, Medtronic agreed that a sham  
8 implant was not merited in this highly refractory  
9 population. And more importantly, because patients  
10 during test simulation become very attuned to the  
11 sensations of stimulation, which involves sensations  
12 of pulling in the rectum, of tingling or vibration in  
13 the perineal or genital region, it logically follows  
14 that in an implant setting, these feelings are nearly  
15 impossible to mask. Therefore, alternative study  
16 designs such as randomizing to on-off, or suboptimal  
17 versus optimal, were reviewed but rejected by the  
18 study investigators.

19 We received FDA clearance for three  
20 different indications, but these indications followed  
21 the same protocol, used the same devices, the same  
22 outcome measurements. And because of rapid  
23 enrollment, an FDA expedited review of Medtronic's  
24 PMA application, Medtronic received clearance in  
25 September of '97 for the indication of urge

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1 incontinence. Shortly thereafter, in April of '99,  
2 the additional indications of urge frequency and  
3 retention also received FDA clearance.

4 And to characterize the chronic safety and  
5 effectiveness of SNS therapy, Medtronic continues to  
6 sponsor an ongoing five-year post-approval study, and  
7 those results are still being collected. I am  
8 available for questions and I thank you for your  
9 attention.

10 MS. CONRAD: Thank you, Dr. Oleson. I  
11 have been asked to continue with the public  
12 presentations and skip the break; just leave the room

13 as you wish to. This will move the HCFA and Blue  
14 Cross presentation back just a little but, but I  
15 think the panel meeting will flow smoothly. I also  
16 wish to tell you that we are going to have a working  
17 lunch, in that the panelists will be leaving around  
18 noontime, getting their lunch and bringing it back  
19 here. They will reconvene at 12:30, not one o'clock.  
20 At 12:30 we will start with the additional public  
21 presentations, if there are any, and then open panel  
22 deliberations. Okay.

23 Having said that, Dr. Steven Siegel,  
24 followed by Dr. Thomas Benson.

25 DR. SIEGEL: Hello, panel members, and

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1 thank you for the opportunity to present this  
2 information to you. My name is Dr. Steve Siegel, and  
3 I am a practicing urologist from St. Paul, Minnesota.  
4 And I have been a paid investigator by Medtronic, I'm  
5 a proctor, I provide educational courses for them,  
6 and my travel to this meeting has been paid for by  
7 Medtronic.

8 My interest in sacral nerve stimulation  
9 for voiding complaints developed from my areas of  
10 subspecialization in female urology and neurourology.  
11 This form of treatment has made a huge difference in  
12 the quality of life of my patients, and you have  
13 heard this again and again from the people that have  
14 spoken ahead of me. These are patients who otherwise  
15 would have had no satisfactory alternatives, and  
16 that's why I've been involved now for over 12 years  
17 in all aspects of this therapy, including  
18 participation in multi-center clinical trials in the  
19 1980s, before Medtronic became involved with the  
20 therapy.

21 I helped to convince Medtronic to sponsor  
22 further trials, I participated in those trials, and I  
23 presented the clinical data to help gain FDA approval  
24 for this therapy in 1997. Since 1997, I have  
25 dedicated much of my personal and professional time

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1 to teaching and training my urologic and  
2 urogynecologic colleagues about SNS in order to help  
3 them provide the treatment for their patients. It's



4 been a great pleasure for me to sit here and listen  
5 to all the physicians who I either had an opportunity  
6 to train in formal didactic sessions, or in the  
7 majority, to participate hands on in one or two of  
8 the initial phases of their first patients.

9 I see this meeting as another opportunity  
10 to document the effectiveness of the therapy for my  
11 patients. My presentation today will provide  
12 information in five areas, the results of the  
13 clinical study, the safety, the impact on quality of  
14 life, the long-term results, and the results of a 65  
15 and older patient survey for patient satisfaction. I  
16 have a lot of information to cover, so please bear  
17 with me if I speed along through it.

18 The study enrolled 581 patients for all  
19 three indications combined. The age range was very  
20 wide, averaging 43 years. The demographics basically  
21 reflect that which is seen in our clinical practice.  
22 And it's amazing to note that the average duration of  
23 symptoms of these patients was eight years. Out of  
24 the 581 patients, 260 experienced at least a 50  
25 percent improvement in one of the primary voiding

00080  
1 measures during the test stimulation, and as Kim  
2 showed you, were randomized into the trial. In  
3 total, 219 patients were ultimately implanted with  
4 the neurostimulation system at the time of database  
5 analysis.

6 It's important to note that the patients  
7 in this study were extensively treated for their  
8 voiding dysfunction, and almost a hundred percent had  
9 some previous form of intervention. The vast  
10 majority had tried and failed multiple drug regimens.  
11 About half had some nonsurgical treatment such as  
12 biofeedback and as you see, the frequency of this  
13 treatment went as high as 147 individual treatment  
14 episodes for a single patient. Almost 60 percent had  
15 some surgical intervention that ranged from a low of  
16 one to a high of 41 procedures for one patient.

17 So it's accurate to say this population  
18 was refractory to traditional treatment approaches,  
19 and had no other treatment alternative other than  
20 nonreversible surgery.

21 Let's talk about the results for urge  
22 incontinence. As indicated, there were 184 patients.  
23 At baseline these patients had an average of 8.9  
24 leaks per day and 2.7 heavy leaks, and those were  
25 defined as saturating pads or diapers, or their

00081

1 clothing. They used an average of 4.8 pads or  
2 diapers per day, and they had a symptom duration of  
3 over nine years.

4 This is the data that compares those  
5 patients randomized to the control group for a delay  
6 of six months to those with an implanted sacral nerve  
7 stimulation system for six months. In all cases, the  
8 control group is in the darker color and the implant  
9 or treatment group is in the lighter color. As Kim  
10 described, the primary measures were the number of  
11 leaking episodes, the severity of the leaking and use  
12 of pads. As you will see for all the measures,  
13 sacral nerve stimulation produced statistically  
14 significant changes compared to control.

15 For the implant group, 47 percent were  
16 dry, and another 29 percent had at least a 50 percent  
17 improvement in their leaking. So in total, 76  
18 percent were considered clinically successful, while  
19 74 percent of the control group had no reduction in  
20 their leaks.

21 As you recall from our definition of heavy  
22 leaking, which was soaked pads or diapers or  
23 undergarments. For heavy leaking, 92 percent of the  
24 treatment group were considered clinical success,  
25 while the control group witnessed few reductions.

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1 The implant group showed a statistically significant  
2 improvement in the number of leaks and number of pads  
3 compared to the control group as well.

4 Just like the preceding slides, the  
5 implant group shows statistically significant  
6 improvements. Here, 50 percent of the implant group  
7 eliminated the need for absorbent pads, and an  
8 additional 37 percent had at least a 50 percent  
9 reduction in pad usage. And as you can see, there is  
10 no corresponding change in the control group.

11 The second population study was the

urgency frequency group, of whom there were 220 patients. Their average number of voids per day were about 13, and they had about 160 cc per void average voiding volume. Their degree of urgency was a 2 on a scale of 1, which was least severe, to 3, which was most severe. And they had an average symptom duration of about eight years.

Just like the previous data, the urgency frequency implant group data is very positive and goes in the same direction compared to the control. For the number of voids per day, 56 percent of the implant group experienced a significant reduction in the number of voids. 64 percent of the implant group experienced a significant increase in the average

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volume per void. The implant group was also clinically successful, with 52 percent experiencing lower urgency and higher volumes, and 36 percent experiencing the same urgency but at higher volumes. Obviously for these patients, the optimal outcome is to have a lower degree of urgency and a higher voided volume.

For the retention group, there were 177 patients who had nonobstructive retention. These patients were basically dependent on a catheter in order to empty their bladder, and they averaged about 335 cc's per catheterization, and they catheterized almost five times per day, and they had a symptom duration of about seven years.

As in the preceding populations, the implant group experienced statistically significant changes. 69 percent of the retention group no longer needed to use catheters. An additional 14 percent experienced a significant reduction in the catheter volume per catheterization and again, you can see virtually no change in the control group. With the sacral nerve stimulation therapy, retention patients voided significantly more and correspondingly, catheterized less.

To document the efficacy of the

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stimulation on versus off and further document the effectiveness of SNS on voiding function, a therapy

3 evaluation test was conducted at six months  
4 post-implant. The stimulation was temporarily turned  
5 off for three to seven days, and voiding diaries were  
6 again collected to compare the effects of the  
7 therapy. Results during the therapy evaluation test  
8 demonstrated a return towards baseline symptoms for  
9 all three groups when the stimulation was turned off.  
10 In all three groups, these changes were statistically  
11 and clinically significant and were similar to  
12 symptoms exhibited at baseline. This clearly  
13 indicates that the reduction of urinary symptoms  
14 observed with stimulation turned on is attributable  
15 to the therapy itself and the therapy is clearly  
16 reversible.

17 Here are the results for the urge  
18 incontinent group, where you can see that at  
19 baseline, they voided almost 11, had 11 episodes of  
20 incontinence per day, versus 2.9 with stimulation on.  
21 And then with it off, went back up towards the  
22 baseline. The results for the urgency frequency  
23 group shows the number of voids at baseline of 16,  
24 down to less than nine, and then back towards  
25 baseline with stimulation turned off. And lastly,

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1 retention, volumes per catheterization decreased  
2 markedly with stimulation on, and increased toward  
3 baseline with stimulation turned off.

4 Next, I want to talk about the safety  
5 data. Safety results were based on a combination of  
6 information from all three study groups, including  
7 urge incontinence, urgency frequency, and retention.  
8 This was permitted as the identical devices and  
9 protocols were used for all three groups. For the  
10 test stimulation procedure, there were 181 adverse  
11 events out of the 914 test stimulation procedures.  
12 The most common event was migration of the lead,  
13 resulting in loss of stimulation during the test  
14 period. This frequently resulted in a repeat of the  
15 procedure so that a solid determination could be made  
16 about any change in symptoms from stimulation.

17 Since the study, the test lead has been  
18 redesigned to a coil design, which is intended to  
19 minimize the potential for lead migration. There

were no long-term clinical sequelae from any of the events, and all adverse events were resolved with no permanent injury to nerves.

Of our 219 implanted patients, 52 percent experienced an adverse event, which ranged from pain at the site of the neurostimulator, infection or skin

problems, to minor concerns such as skin irritation. 91 percent of the events were resolved at the time of original study database closure. It's important to note that no event resulted in a permanent nerve injury.

A little more than half of the adverse events required some surgical intervention. This included repositioning of the neurostimulator due to pain. It's now most often implanted in the upper buttock instead of the lower abdomen in order to reduce this risk, and also, revisits included repositioning of the lead due to migration. The lead was redesigned to permanently attach the anchor to the lead body, which is intended to reduce lead migration. I will discuss a little bit more about that in a moment.

Next I want to emphasize the quality of life data. We used the SF-36 Health Outcomes Survey, which as you know, is a validated measurement tool for collection of quality of life information. The following three charts compare the implant group which is in blue, with the control group in red, and US normative data is on the top in light green. For each of the eight scores, the range is between 0 and 100, and as you can see from the normative data, even

a healthy person doesn't rate everything at a hundred percent.

For urge incontinent patients there were significant improvements reported in several of the categories. You can note the differences between the implant group and control group that were statistically significant in both physical functioning, general health and vitality.

The most dramatic changes were seen in the urgency frequency patients, and they had significant

improvements in many of the categories. These patients showed scores that were significantly higher than the control group on seven of the eight variables. For all three populations studied, this was clearly the group that was most negatively impacted by the baseline symptoms and most dramatically improved with sacral nerve stimulation.

For retention patients, there were statistically significant differences seen in the scores for bodily pain.

Overall, the clinical study showed that sacral nerve stimulation provided to a refractory group of patients resulted in a statistically significant improvement in primary voiding measures. And these improvements were also accompanied by

significant improvements in the various domains of the SF-36 outcome survey.

While I mentioned device improvements during the adverse events information, I want to recount the specific device advancements that have been made as a result of the clinical study. Difficulty with migration of the test lead during the test stimulation period led to development of a coiled wire design for the lead. The intention of the design is that it uncoils to stretch before displacing. The new test stimulation lead design uses a nondiscrete electrode, which eliminates the possibility of separation by advancing the foramen needle over the lead after it's been inserted. Additionally, adverse events experienced led to the development of a change in the implant lead. Originally, the anchor used was separate from the implant lead, and now we use a preattached fixation point to avoid snaking of the lead or lead migration.

Next, I want to show you the long-term results from all three study populations. Consistently, there were sustained clinical results for urge incontinence. These are the percentage of patients who have a greater than 50 percent reduction in leaks per day as you can see now, out to 48

months. For urgency frequency, over half the

2 patients have a 50 percent or greater increase in the  
3 volume voided per void now followed out to 36 months.  
4 And for the retention patients, more than 70 percent  
5 of the population have eliminated catheterizations or  
6 are experiencing a 50 percent or greater reduction in  
7 the residual catheterized volume, now out to 36  
8 months.

9 By way of summarizing the study, sacral  
10 nerve stimulation is providing sustained efficacy for  
11 all indications in populations of patients who were  
12 refractory to all other treatment. Sacral nerve  
13 stimulation is safe, it's reversible, and it doesn't  
14 preclude alternative treatment.

15 I know that the panel will want to focus  
16 on how this therapy works for patients over 65 years  
17 of age. To augment the clinical study and long-term  
18 data we just reviewed, a survey of patients 65 and  
19 over was undertaken. 140 patients in Medtronic's  
20 device registry over 65 years were sent a survey  
21 about their experiences with SNS, and 68 provided  
22 responses, and here's what was learned. The median  
23 age of the respondents was 73, and over 90 percent  
24 reported that they had urgency frequency or urge  
25 incontinence as the reason for the SNS implant. Like

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1 patients in the clinical study, the responders had  
2 experienced voiding dysfunction symptoms for a median  
3 of eight years. Nearly 100 percent indicated that  
4 their physician recommended over treatments prior to  
5 SNS implant, and about 60 percent had some type of  
6 surgery for their bladder problem. They indicate the  
7 following. 93 percent are using the implanted  
8 system. 75 percent are satisfied with the results.  
9 The median improvement in symptoms was 70 percent.  
10 87 percent would recommend the therapy to others.  
11 And 84 percent would repeat the surgery. Overall,  
12 two-thirds of them are using the system, are  
13 satisfied, would recommend it to others, and would  
14 repeat the surgery. Clearly, there are substantial  
15 results and satisfaction among Medicare aged patients  
16 regarding sacral nerve stimulation.

17 In conclusion, I would like to point out  
18 that this is a very clinical presentation of a

19 scientific study that I think shows that there were  
20 dramatic and positive results in the management of  
21 these patients' refractory clinical syndromes and  
22 that impact their quality of life greatly. You've  
23 heard many of the physician presenters who are  
24 motivated to come here on their own behalf, speak of  
25 specific clinical instances from their own practices,

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1 which are very compelling, and that's what I would  
2 like to point out to you, that each one of these data  
3 points discussed today represent an individual who  
4 has had their great suffering alleviated dramatically  
5 by this therapy. And I appreciate very much the  
6 opportunity to bring this to your attention in the  
7 hopes that it will become available for patients in  
8 the Medicare age population. Thank you.

9 MS. CONRAD: Thank you, Dr. Siegel.

10 DR. MAVES: Dr. Siegel, this is a very  
11 well done study. Can you help me with some numbers,  
12 because I'm having a little trouble following some of  
13 the patient numbers, and just sort of help me with  
14 this.

15 DR. SIEGEL: Sure.

16 DR. MAVES: You start out saying you have  
17 581 patients total involved in the study, of which  
18 219 received implants. But then when we go back  
19 through, for instance when you look at the urge  
20 incontinence, for instance, I think it's hard to sort  
21 of say that the number of implants that you were  
22 looking at when you said there's a 76 percent  
23 clinical success, there's only 34. And similarly,  
24 when you go back through the other categories,  
25 retention, I think there was 29 implanted, and for

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1 the urge frequency, 25 implanted. So the numbers  
2 sort of deteriorate.

3 And then when we get back to looking at  
4 some of the other factors in the end, such as the  
5 long-term results of urge, urge frequency and  
6 retention, the numbers seem to go back up. Explain  
7 to me sort of the rationale and how to follow that,  
8 because you sort of start out with a big N and you go  
9 gee, you've got some real power here. It seems to go



10 down when you're looking at the categories and then  
11 reappears.

12 DR. SIEGEL: That's an accurate  
13 observation, and basically it has to do with the  
14 design of the study. We had the large number of 500  
15 some odd patients to begin with. Those were all the  
16 patients who underwent a test stimulation. Of that  
17 group of patients, roughly 50 percent, or 260,  
18 actually had at least a 50 percent improvement in one  
19 of the key symptom variables for whatever category  
20 they were being enrolled in the study in, so that's  
21 where that half of the patients went.

22 Now, in the study design where there is a  
23 control arm and an immediate implant arm, in each  
24 individual category, the total pool of patients that  
25 were going into the urgency frequency group were

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1 split in half again, and so you're looking at the  
2 half of the patients that were implanted versus the  
3 half of the patients that served as control. So  
4 there again is where that N decreases.

5 Now, in the longer term study arms, what's  
6 happening is that some of those patients that were in  
7 the control arm, actually virtually all of those  
8 patients were then given the option to go on to  
9 implantation, so they matriculated into the  
10 implantation arm and you're seeing those patients  
11 again in terms of the long-term study.

12 DR. OLECK: I have I guess a follow-up  
13 question on that, and I have a couple of other  
14 questions. Beyond what you describe here though,  
15 when I was looking, and some of these numbers come  
16 from the TEC assessment, I guess they had looked at  
17 more things that were just in the articles there. It  
18 looked like there were a number of case, for example  
19 in the urge incontinence, I think they had said there  
20 were 98 patients that were randomized and yet, the  
21 report was only on 76 of them. In the urge frequency  
22 study, there were 80 eligible and the report was only  
23 on 51 of them.

24 In going through the report, well,  
25 primarily the TEC assessment, it looks like, first of

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1 all, there were some people who were randomized, a  
2 good number of people who were randomized to the  
3 implant group who didn't have the implant. There  
4 were also a number of people who said well, they  
5 didn't have data at six month because the study was  
6 closed out before they reached that six months. I  
7 mean, that is really surprising to me that in a study  
8 which is supposed to define the usefulness of this,  
9 that the study was closed out before the six-month  
10 variable or the six-month end point for such a large  
11 number of people. Can you explain that?

12 DR. SIEGEL: That is what happened, in the  
13 sense that when this data was presented to the FDA in  
14 1997 and that data was used as a basis for some of  
15 the initial publications for the efficacy in urge  
16 incontinence, not all the patients had been implanted  
17 and followed out to six months, and therefore, they  
18 were not included in that database analysis, so  
19 that's what that statement meant.

20 And as far as other patients that were  
21 randomized to the implant phase that did not go on to  
22 implant, I am not aware of what the specific  
23 percentage of patients that represented, but my  
24 honest impression is that it was a very minute  
25 percentage and indeed as I emphasized, virtually all

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1 of the patients who were randomized to the control  
2 arm ultimately went on to be implanted.

3 DR. OLECK: I guess the other question I  
4 had concerns the exclusion for the neurological  
5 patient, in terms of why those were excluded, whether  
6 there was some idea those people would respond  
7 differently to that. Apparently there wasn't any  
8 formal mention made of that exclusion in the FDA  
9 approval. Does that mean this shouldn't be used in  
10 those patients, or can you explain that.

11 DR. SIEGEL: Well, that has to do with the  
12 strategy of the study to gain FDA approval. In other  
13 words, we want to pick cherries and show that we can  
14 bake a cherry pie. And so what we wanted to do is  
15 pick the most clear-cut individuals that would have  
16 the greatest chance of success. That doesn't mean  
17 that individuals who have an underlying neurological

18 disorder might not improve, but say for example  
19 patients with M.S., which is a disease that the  
20 symptoms may wax and wane, if we implant the patient  
21 who had M.S. And then the therapy became less  
22 effective for that patient, does that represent a  
23 primary failure of the therapy or does it represent  
24 the fact that the target disorder is changing. And  
25 we didn't want to have to answer those questions in

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1 order to gain the FDA approval.

2 At this point, there is good clinical  
3 expectation that those patients would improve and  
4 they should be the subject of further study to  
5 document the effectiveness in specific patient  
6 populations, like partial spinal cord injury, or  
7 M.S., Parkinson's, et cetera.

8 DR. OLECK: It seems if we're talking  
9 about neruomodulation to people who have neurological  
10 diseases, if it doesn't apply to them, that would  
11 seem to be a significant group to raise a number of  
12 questions about whether it would or it wouldn't be  
13 effective or as effective in that group of people.

14 DR. SIEGEL: What I would say again as an  
15 answer to that question is that I believe personally  
16 that this therapy would help a significant proportion  
17 of those patients. And as a scientist, I believe  
18 that it needs to be demonstrated with well designed  
19 clinical studies that those patients are impacted  
20 with the therapy.

21 DR. GARBER: Ken?

22 DR. BRIN: I wonder if we could focus for  
23 a minute on the Medicare population. How many of the  
24 patients in the original study were of age 65 or  
25 older, have you done a subgroup analysis, did these

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1 patients tend to be the ones who had greater  
2 complication rates, were the success rates identical,  
3 worse, better, can you share with us some of that  
4 data?

5 DR. SIEGEL: I think I can share with you  
6 that data. We had -- I believe there were eight  
7 patients?

8 DR. GARBER: Yeah. Miss Oleson, you can

9 respond if you'd like.

10 MS. OLESON: There were nine subjects who  
11 had 12-month follow-up in the clinical study who were  
12 age 65 years and older. And I believe at the most  
13 recent administrative closure, we have about 50  
14 percent of those patients demonstrating a 50 percent  
15 or greater improvement in their symptoms, so it  
16 appears to be consistent. If you look at other  
17 prognostic factors, just by looking at age  
18 categories, we found that age is not a prognostic  
19 factor in terms of potential for success, so we have  
20 concluded from looking at that factor as well as  
21 others, including potential for revision surgery,  
22 duration of symptoms, number of test stimulations,  
23 et cetera, that basically test stimulation appears to  
24 be the one factor that helps to select patients which  
25 are more amenable to surgery.

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1 DR. GARBER: Well, maybe I could ask Ken's  
2 question in a slightly different way. Two of your  
3 slides, Dr. Siegel, were about the safety data, the  
4 test stimulation based on implantation. There were  
5 914 patients in the test stimulation phase and you  
6 didn't give the number for implantation, but  
7 presumably this is larger than the clinical trial  
8 because there were more people in the implantation  
9 test.

10 DR. SIEGEL: No, I didn't mean to  
11 represent it in that way. There were 914 test  
12 simulations performed on the 500 patients.

13 DR. GARBER: On the same sample.

14 DR. SIEGEL: Right. So it means that some  
15 of the patients had two test stimulations.

16 DR. GARBER: Do you happen to have the  
17 data that appear in the (inaudible) follow-up  
18 implantation stratified by age. The subsequent table  
19 is the one that said 15.3 percent had pain at  
20 neurostimulator site, 9 percent in pain, et cetera.

21 MS. OLESON: I'm trying to understand.

22 DR. GARBER: Divided by age above or below  
23 65, for example.

24 MS. OLESON: We have looked at as a cutoff  
25 age of 59 because we had so few patients who were 65

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1 and older.

2 DR. GARBER: That's fine.

3 MS. OLESON: And are you looking at the  
4 potential for efficacy?

5 DR. GARBER: No, this is only safety data,  
6 so it's the adverse effects associated with the  
7 implantation. I'm just curious if the rates differed  
8 in any systematic way.

9 MS. OLESON: No, they did not.

10 DR. GARBER: Okay, thank you.

11 DR. OLECK: And commenting further on the  
12 age thing, I guess, we've heard a lot about how this  
13 does seem to be a problem affecting, urinary  
14 incontinence affecting the Medicare age population.  
15 I guess I'm just surprised that, why the study  
16 population was then so heavily weighted or was more  
17 heavily weighted to a younger population rather than  
18 to the Medicare age population.

19 DR. SIEGEL: Well, this is a classic  
20 catch-22 in the sense that we were expected in  
21 performing this clinical study to obtain insurance  
22 reimbursement for the patients that participated in  
23 the study, and patients that were 65 years of age or  
24 older were not allowed to participate in a clinical  
25 experiment. So for that issue, we didn't enroll

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1 those patients and that was basically the reason.

2 DR. GARBER: Ken.

3 DR. BRIN: Just a question with regard to  
4 learning curve and complication rates. Have you  
5 analyzed your study data to take a look at whether  
6 complication rates decrease substantially with number  
7 of procedures by the surgeon performing this, or is  
8 it randomly distributed?

9 MS. OLESON: The revision rates were  
10 equally distributed amongst investigative sites. We  
11 also looked at the early implants versus the later  
12 implants, and there was no statistical difference  
13 observed.

14 DR. SIEGEL: I can just say from my own  
15 clinical experience now with over 12 years of this  
16 therapy, and witnessing many of my colleagues getting

17 started with the therapy, that there is a substantial  
18 learning curve and that both issues of patient  
19 selection and the risk of complications associated  
20 decrease with the experience of the physician.

21 MS. CONRAD: Thank you, Dr. Siegel.  
22 Dr. Benson, please, followed by Martha Goldberg  
23 Aronson.

24 DR. BENSON: Good morning. My name is J.  
25 Thomas Benson. I'm a urogynecologist in

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1 Indianapolis, Indiana. I'm at the University of  
2 Indiana and I direct a urogynecology fellowship. The  
3 fellowship is actually in female pelvic medicine and  
4 reconstructive surgery. This fellowship is three  
5 years in duration and it's accredited by the American  
6 Board of Obstetrics and Gynecology, and by the  
7 American Board of Urology, I think probably the first  
8 time a fellowship has had double board accreditation.  
9 It's open to graduates of either OB/Gyn residencies  
10 or urology residencies, and at the end of their  
11 four-year residency or five-year residency, they come  
12 and spend three more years in fellowship. So it's a  
13 lot of training. So our patient population are women  
14 with pelvic floor disorders. It's tertiary in that  
15 almost all of our patient have failed surgeries  
16 elsewhere and end up coming to us for care.

17 In this overview I would like to tell you  
18 how we select patients for sacral nerve stimulation  
19 therapy, describe three representative cases from our  
20 practice, and discuss what we can learn from these  
21 cases.

22 First off, when a patient comes to us with  
23 this problem, even though it's tertiary, we will  
24 still begin with the less interventional techniques.  
25 Diagnosis is established first to determine if the

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1 patient has stress incontinence, urge incontinence,  
2 or a combination or some other disorder. Then  
3 behavior modification is employed, behavior  
4 modification including diary, examinations, examining  
5 what they take in, fluid intakes, et cetera,  
6 modifying caffeine intake, smoking, so forth. Then  
7 pelvic floor rehabilitation is carried out with

8 either biofeedback or functional electrical  
9 stimulation, and most of that care is performed by  
10 physical therapists that work with us in our group.  
11 Then the patients most often will go through  
12 pharmaceutical management if they have not had  
13 improvement with the behavior modification and pelvic  
14 floor rehabilitation efforts. And then  
15 pharmaceutical managements lead to a fair degree of  
16 success.

17 The ones that have failed all these then  
18 are candidates for sacral nerve stimulation testing.  
19 That is our algorithm for getting to these patients.  
20 Otherwise, these patients who have failed all these  
21 other therapies would be thinking of a very invasive  
22 surgery such as bladder augmentation.

23 Three examples of our patients: Patient  
24 HS, this person is a personal physical trainer.  
25 She's from Germany, very proud of her physique, she's

00103  
1 41 years old, but she has severe disorder.  
2 Interstitial cystitis was her diagnosis, and she had  
3 had two bladder augmentation surgeries, trying to  
4 increase this. She had had several hospitalizations  
5 for bladder hyperdistention prior to the bladder  
6 augmentation surgeries. Because of the bladder  
7 augmentation surgeries, the detrusor muscle was  
8 removed, and so she was unable to void on her own,  
9 and so she had to self catheterize. She self  
10 catheterized 30 times a day, seven to eight times t  
11 night; she had never slept more than 45 minutes at  
12 this time.

13 She was so severely depressed by this, she  
14 could not work, could not do an activities, and  
15 seriously was contemplating suicide, was under  
16 psychiatric management for this. She learned about  
17 sacral nerve stimulation on the Internet and obtained  
18 a referral, and she had a dramatic response to the  
19 test stimulation. She went to seven voids per day,  
20 seven catheterizations per day. She had no nocturnal  
21 episodes of having to get up to catheterize. She of  
22 course cannot empty her bladder because she doesn't  
23 have a detrusor, but now she has a normal life with  
24 seven to nine self catheterizations per day.

25                   Next patient, SH is a 28 year old female

00104

1     patient who had inability to urinate. She had  
2     nonobstructive urinary retention. She also had a  
3     severe constipation disorder that in this young 28  
4     year old led to a colostomy. She would self  
5     catheterize for urinary retention beginning when she  
6     was 16 years old, had never voided on her own since  
7     that time. With her test stimulation results she was  
8     able to urinate voluntarily. We implanted her over  
9     two years ago and she has never self catheterized  
10    since that time. She even had the colostomy taken  
11    down.

12                The next patient is RE, which is sort of  
13    typical of the group over 65; a very frequent  
14    condition in people over 65 is a condition called  
15    DHIC, detrusor hyperreflexia with inadequate  
16    contractility. So these poor unfortunate ladies  
17    cannot empty their bladder well and yet it's  
18    constantly emptying on its own when they don't want  
19    it to. So they have both ends of the problem. This  
20    particular patient had a combination of the retention  
21    urge incontinence, and she'd had four surgeries for  
22    incontinence at various points in her life and had  
23    failed medical management. Her diary showed 14 voids  
24    per day, four self catheterizations, three to four  
25    heavy leaks requiring her to wear diapers.

00105

1                With her test stimulation results, she  
2    went down to one leaking episode per day, did not  
3    have to self catheterize, and had a frequency of nine  
4    to ten voids per day. At 12 months post-implant, she  
5    has no accidents, does not have to self catheterize,  
6    and has nine voids per day.

7                We can learn a lot from these cases. We  
8    can even start getting an idea, and are doing a lot  
9    of investigational work trying to figure out why this  
10   therapy works so well. We still don't know the exact  
11   answers, but we do know that it has a lot to do with  
12   the reflex pathways in the pelvic floor, it has an  
13   awful lot to do with the afferent pathway, not just  
14   the motor pathway. And several studies are showing  
15   this and coming together to show how it changes



16 sensory thresholds, showing how it works better in  
17 people that have intact pelvic floor reflexes,  
18 et cetera.

19 The bottom line though for physicians and  
20 for the patients, is what a difference this makes in  
21 their lives. You have heard that over and over this  
22 morning and I would add to that, I have been doing  
23 this kind of work now almost 30 yours and I would  
24 have to say this is probably the single most  
25 gratifying therapy that I have been able to have to

00106  
1 use for my patients, because this group is so  
2 difficult to treat otherwise. Thank you.

3 MS. CONRAD: Thank you, Dr. Benson. Okay,  
4 finally, Martha Goldberg Aronson.

5 MS. ARONSON: My name is Martha Goldberg  
6 Aronson and I am the general manager of Medtronic  
7 functional stimulation. I want to very briefly  
8 review several important topics, including physician  
9 training, evaluation and adoption of sacral nerve  
10 stimulation.

11 As you have already heard this morning, as  
12 part of the FDA approval, Medtronic is required to  
13 thoroughly train physicians in the use of SNS. The  
14 approval requires that SNS be prescribed only by  
15 physicians experienced in the diagnosis and treatment  
16 of lower urinary tract symptoms, or urologists and  
17 urogynecologists. Medtronic trains these physicians  
18 through a didactic one and a half day classroom  
19 training course which includes cadaver work, and that  
20 is then followed by the proctorship process, whereby  
21 a proctor stands next to the physician for their  
22 first two test stimulation procedures and then again  
23 is proctored for the first two implant procedures.  
24 And this is done, performed by a physician who is  
25 experienced in utilizing sacral nerve stimulation.

00107  
1 Additionally, we have on-site training  
2 centers available if a physician requires or requests  
3 additional training on the therapy. So far, 538  
4 physicians have attended a workshop. We estimate  
5 that we will continue our training efforts with an  
6 anticipated 200 additional physicians to be trained

7 each year. Currently, 189 have fully completed the  
8 proctoring program and are actively using the therapy  
9 in their practice, and 88 physicians are in the  
10 process of proctorship.

11 We are very pleased with the enthusiastic  
12 adoption of sacral nerve stimulation by the physician  
13 community. Later today you will be hearing from  
14 Dr. Lefevre from the Blue Cross/Blue Shield  
15 Technology Evaluation Center on reported evidence on  
16 sacral nerve stimulation. I think it's also  
17 important to know about the level of scientific  
18 scrutiny by other technology assessment  
19 organizations. In addition to Blue Cross/Blue Shield  
20 assessments, SNS has been evaluated by Hayes, ECRI,  
21 and numerous payor organizations.

22 For the record, Medtronic requested that  
23 the panel address all three indications. We  
24 acknowledge that HCFA has only asked the panel to  
25 address two indications, urge incontinence and

00108  
1 urgency frequency. Our understanding and our request  
2 is that HCFA consider all three indications, urge  
3 incontinence, urgency frequency, and retention in its  
4 coverage policy considerations. This substantial  
5 level of evaluation has been fueled by a high level  
6 of publication. Since early 1999, 19 peer review  
7 articles have been published or accepted for  
8 publication. SNS has also been the subject of  
9 numerous abstracts, posters, and presentations at  
10 scientific meetings. This has served to increase  
11 awareness as well as adoption of the therapy.

12 As evidence of this, you can see that  
13 commercial payors have made positive coverage  
14 decisions on hundreds of SNS cases. Over 60 have  
15 issued a written coverage policy. Further, local  
16 medicare jurisdictions have been active in providing  
17 coverage, 34 have issued positive coverage policies,  
18 13 provide individual case coverage, and three  
19 jurisdictions are developing coverage policies, for a  
20 total of 50 out of 52 jurisdictions. Almost all  
21 Medicare beneficiaries have access to this therapy.  
22 Thank you very much for your time and attention.

23 MS. CONRAD: Thank you, Miss Aronson.

24 DR. OLECK: Question. I don't know if you  
25 can answer or one of the other people. In terms of  
00109

1 other conditions that are being looked at now besides  
2 the three that are listed, are there active studies  
3 looking at this for other conditions, particularly,  
4 it was mentioned to me before, the neurological  
5 patients, but I was wondering for stress incontinence  
6 or the primary pelvic pain patients that were one of  
7 the exclusions, or other things.

8 MS. ARONSON: The most active trial going  
9 on right now is utilizing sacral nerve stimulation  
10 for bowel disorders. There is an active study group  
11 underway with that and in fact we do have CE mark  
12 approval for that device to be utilized for that in  
13 Europe, so that is underway. There are also other,  
14 we have a small study underway to look at the  
15 effectiveness of sacral nerve stimulation in the  
16 multiple sclerosis population, and in addition, we  
17 are aware of some additional physician sponsored work  
18 that is going on, but those would be the two main  
19 areas that Medtronic is involved in.

20 DR. OLECK: Thank you.

21 MS. CONRAD: Thank you. Continuing with  
22 the program, Dr. Mitch Burken.

23 DR. BURKEN: Good morning. My name is  
24 Mitchell Burken and I'm a medical officer with the  
25 HCFA coverage and analysis group. I'd just like to

00110  
1 say, or I'd like to embellish some of Ms. Doherty's  
2 earlier points before turning the program over to  
3 Dr. Frank Lefevre of the Blue Cross/Blue Shield  
4 Association, however, the intervening public speaker  
5 have also included this information.

6 I think we've seen this diagram earlier in  
7 some slightly different forms, but here we go, here  
8 we have the pulse generator that's implanted  
9 subcutaneously, wire passing through the sacral  
10 foramen and enervating the sacral nerve roots, and  
11 there's multiple points of enervation, but most  
12 notably the bladder.

13 Urge incontinence, as we have discussed  
14 earlier, is the involuntary loss of urine associated

15 with a strong desire to void, and this is urgency,  
16 and it's usually associated with involuntary  
17 contractions of the detrusor muscle. Such detrusor  
18 instability can occur in both individuals with and  
19 without specific neurological disorders.

20 The urgency frequency syndrome is well  
21 described in the article by Brubaker and Sand from  
22 1989. Urgency frequency syndrome is the  
23 multifactorial presentation of urinary frequency,  
24 that is, voiding intervals of two hours or less, or  
25 more than seven times per day, combined with urgency,

00111

1 which is a powerful sensation to void regardless of  
2 bladder volume. Patients may have easily treatable  
3 causes such as uncomplicated cystitis. However,  
4 bladder neoplasm or interstitial cystitis may have  
5 the same presenting symptoms. The increasing  
6 incidence and prevalence with age is due to several  
7 factors such as atrophic changes in the epithelium  
8 and the muscle composition of the urethra, as well as  
9 the predilection for iatrogenic causes such as  
10 catheterization and other instrumentation.

11 Now, I have a working definition of  
12 refractory. It's important to note that this term  
13 refractory is very central to the charge of the MCAC  
14 today, and as a working definition, the patient has  
15 already failed an attempt at one or more of the  
16 following modalities: Behavioral therapy such as  
17 prompted voiding or pelvic muscle exercises;  
18 pharmacology such as anticholinergics; and surgery.  
19 And earlier speakers have gone into these therapies  
20 in more detail.

21 Finally, I just wanted to make the point  
22 that the MCAC packet includes different types of  
23 evidence, it includes the clinical trials data which  
24 has been described and which Dr. Lefevre will also go  
25 into. But there is also case series data which is in

00112

1 your packet, along with some tables which summarize  
2 those case series reports. On the right-hand side of  
3 the diagram is an alternative approach where clinical  
4 trials data is used only and other approaches are set  
5 aside and not reviewed.

6 Thank you, and Dr. Lefevre will follow.

7 MS. CONRAD: I invite Frank Lefevre to the  
8 microphone please. Thank you, Dr. Burken.

9 DR. LEFEVRE: I want to thank the panel  
10 for the opportunity to present our assessment of this  
11 technology today. My name is Frank Lefevre from Blue  
12 Cross/Blue Shield Technology Evaluation Center, and  
13 also from Northwestern University.

14 The objective of our assessment was to  
15 determine whether sacral nerve stimulation improves  
16 health outcomes for patients with refractory urge  
17 incontinence and urgency frequency syndrome. We used  
18 an evidence based approach to perform this objective  
19 and we will look today at the adequacy of the  
20 evidence, both considering the methodological quality  
21 of the evidence and the magnitude of effect, and we  
22 will also consider the relevance to the Medicare  
23 population.

24 Just a brief word about the Blue Cross TEC  
25 center. It's one of the longest standing and most

00113  
1 well established technology assessment bodies.  
2 Established in 1985, has to date performed over 400  
3 full length technology assessment reports, and  
4 follows established rigorous methodology for evidence  
5 based medicine, which includes external review by our  
6 medical advisory panel, and this assessment has been  
7 reviewed and approved by our medical advisory panel.  
8 The TEC program has established partnerships with  
9 Blue Cross plans as well as with Kaiser Permanente  
10 since 1993, and since 1997 has been one of the 12  
11 evidence based practice centers of the AHRQ. This  
12 reflect an evolution of the TEC program from an  
13 entirely proprietary organization in the 80s to a  
14 more publicly available program, and in fact the TEC  
15 program will in the next year or two become entirely  
16 publicly available and all the TEC assessments will  
17 be available to the public and to consumers as well  
18 as physicians outside of the TEC program.

19 We used systematic review methodology for  
20 approaching this question and these are the steps  
21 that we follow in this methodology. The first step  
22 is to establish a problem formulation, and the

23 problem formulation in essence will define for us  
24 what are the patient indications for this procedure,  
25 what is exactly the intervention that we are talking

00114

1 about, what are the outcomes that we will be  
2 interested in, and then finally, what are the  
3 comparison technologies that we want to compare this  
4 to.

5           Following the problem formulation, we  
6 would develop a priori study selection criteria which  
7 will define what types of study will be adequate for  
8 answering our question that we posed. Then we would  
9 systematically search the literature for any studies  
10 which meet this selection criteria, we would abstract  
11 the outcome data that we have decided is relevant to  
12 the assessment, and then go ahead and synthesize the  
13 data, either qualitatively or quantitatively,  
14 depending on the data available.

15           The problem formulation for this  
16 assessment includes first of all, the patient  
17 indications and as was stated before, refractory urge  
18 incontinence and refractory urgency frequency  
19 syndrome. We define refractory as patients who had  
20 failed conservative treatment, and under conservative  
21 treatment we would place both behavioral modalities  
22 and drugs. The issue of whether someone should fail  
23 surgery prior to this is questionable, but we didn't  
24 feel that was an appropriate indication to include,  
25 so we defined conservative treatment as drugs and/or

00115

1 behavioral therapies, although many patients who end  
2 up getting this technology have already went through  
3 surgical procedures.

4           The intervention was defined as an  
5 implantable device that delivers controlled  
6 electrical impulses to the sacral nerve roots with  
7 the intent of modulating the neurological input to  
8 the genital urinary system.

9           Now the outcomes we considered important  
10 are listed here. Now the main outcomes in urinary  
11 incontinence are derived from patient recorded  
12 diaries, and when patients mainly record the number  
13 of incontinent episodes or the number of times that

14 they void and then starting from this data, you can  
15 calculate the outcome measures that we have here.  
16 First of all, what's the percent change in the  
17 frequency of incontinence and/or the frequency of  
18 voiding. And this a prepost kind of measure as to  
19 the percentage of change overall.

20 The percentage of patients improved is  
21 often used as another outcome measure, and a 50  
22 percent improvement in incontinence has been defined  
23 by urological societies as a clinically significant  
24 improvement. And so we would agree that percentage  
25 of patients with a 50 percent improvement is a

00116  
1 clinically important measure which can also be looked  
2 at.

3 And lastly and perhaps the most important  
4 measure, the percent of patients who are cured. And  
5 when we're talking about urge incontinence, the  
6 percent of patients who are cured are those who have  
7 no further incontinence. When you're talking about  
8 urgency frequency syndrome, the percentage of  
9 patients who are cured are those that go below a  
10 predefined threshold of what's normal voiding, and  
11 that is typically defined as seven or less episodes  
12 per day.

13 The second category of outcomes, which may  
14 be very important, are quality of measures, and we  
15 will talk about some quality of life measures, the  
16 SF-36 that are included here. And then finally, we  
17 will compare these beneficial outcomes with adverse  
18 events outcomes to determine the net risk-benefit  
19 ratio.

20 The comparison treatments are a bit  
21 problematic in this assessment because of the issue  
22 of the definition of refractory and what are the  
23 appropriate comparisons. For someone who has gone  
24 through all the available treatments, including  
25 surgery, then the appropriate comparison is really no

00117  
1 further treatment, because they really have no  
2 alternatives. However, for patients who have only  
3 completed conservative treatments, meaning behavioral  
4 and pharmacological therapy, then surgical

alternatives are an appropriate comparison group.

Under surgical alternatives there are quite a number of different variations of surgery and I've listed three for here. For urge incontinence particularly, there's the enterocystoplasty, this was referred to as an augmentation cystoplasty. There's also bladder denervation procedures, where the nerve impulses to the bladder are interrupted. And also a newer procedure called detrusor myeloection, where part of the detrusor muscle is taken out. Any of these could be considered a viable alternative to sacral nerve stimulation for certain patients.

Finally, urinary diversion can't be considered a comparison treatment. This is a permanent catheterization or cystectomy with permanent suprapubic catheterization, but this is really not an acceptable alternative for the majority of patients that we will be considering for this treatment.

So, our study selection criteria was full length published literature in the English language,

and it was refractory urge incontinence or urgency frequency patients, and we did require that we would want to see a concurrent comparison group which was not treated with sacral nerve stimulation. This was important because it did exclude many of the case series or clinical series of this technology which are available, but we did not feel that offered strong evidence as to the true efficacy of the procedure. And finally, the reports would have to report on at least one of the relevant outcome measures that we talked about.

And then our key question, just to repeat, is for patients with refractory urge incontinence or urgency frequency syndrome, does treatment with the sacral nerve stimulation improve health outcomes?

Now, there were two articles about the selection criteria, one in each category, and these were both populations drawn from the same multi-center study sponsored by Medtronic. Now we've heard a lot about this study today and I think what I'll try to do in the interest of time is not to



22 spend a lot of time on the results per se; the  
23 results that have been presented are very much the  
24 same as what I have, but try to focus more on the  
25 interpretation of the results from our perspective,  
00119

1 and are they valid and what do they mean.

2           There were several stages to this study,  
3 as was mentioned. First, the test stimulation, the  
4 peripheral nerve evaluation test. Secondly, the  
5 randomized portion, in which sacral nerve stimulation  
6 was compared to a control group, a waiting list  
7 control. This was supplemented with the cohort  
8 analysis, which was a longer follow-up of all  
9 patients who received the technology. And finally,  
10 the therapy evaluation test where the stimulation was  
11 turned off and outcomes were reevaluated at that  
12 point.

13           The patient population defined here, we've  
14 seen some of this data before. Evidence that there  
15 has been extensive prior treatment in these patients,  
16 although the exact prior treatment is not  
17 standardized. Patients may or may not have had  
18 either or any of these treatments. For example, most  
19 patients had drug treatment, almost all the patients  
20 had drug treatment. Somewhat over half had prior  
21 surgical procedures. Somewhat less than half overall  
22 had had nonsurgical procedures, which would include  
23 the behavioral treatment. And the number of prior  
24 procedures are listed here for each of the  
25 categories, an average of over one surgical procedure

00120

1 per patient in the urge incontinence, and over two  
2 surgical procedures per patient in the urgency  
3 frequency group. And also, a significant number of  
4 nonsurgical procedures.

5           The average length of time of symptoms was  
6 between seven and nine years, and the baseline amount  
7 of incontinence or degree of severity of illness was  
8 actually quite high. So I think there is evidence  
9 that this is a severely ill population with extensive  
10 and longstanding prior treatment, even though it's  
11 not totally standardized as to what that was.

12           This was also discussed previously, sort

of the flow of the patients through the study, and I just listed here for each of the categories again, the urge incontinence and the urgency frequency, the number of patients who enrolled in this study; this is the number of patients who were eligible by the eligibility criteria of the study in each category, 155 in the urge incontinence, and 222 in the urgency frequency syndrome. Of these, the second line gives you the number of patients who passed the test, the peripheral nerve test phase, and were randomized. Of the 155 urge incontinence patients, 63 percent of them passed the peripheral nerve test; a total of 98 were eligible for randomization.

And in the urgency frequency group, it was somewhat less. A little more than a third of the patients in this group passed the peripheral nerve test and were eligible for randomization. A total of 80 were eligible for randomization in this group.

And finally, the patients evaluated at six months. This was again, mentioned before, and somewhat less than the number of patients who were randomized. Most of the patients who were randomized but were not evaluated at six months had not reached the six-month time point at the time of the study reporting. It was not truly dropouts; the number of dropouts was somewhat less, I believe it was about 10 percent overall that were true dropouts. So this number of patients evaluated is a subset of the number of patients implanted but it is more a function of who reached the time point at the time the study results were reported.

These were results we have seen before. This is the percent change in incontinence or in voids. For the urge incontinence group it's the percent change in incontinent episodes, number of leaks per day. For the urgency frequency group, it's the change in the number of voids per day. A 73 percent reduction for the urge incontinence group in

the number of leaks per day, compared to a 22 percent worsening in the control group, statistically significant at 0.00 -- less than 0.0001. Somewhat

4 less impressive results for the urgency frequency  
5 group, with a 45 percent overall reduction in the  
6 number of voids per day compared to virtually no  
7 change in the control group, again, statistically  
8 significant at the same level.

9 The two other outcomes, the percent of  
10 patients improved, again meaning the percentage of  
11 patients with a greater than 50 percent improvement,  
12 percentage of patients cured, 76 percent of the  
13 patients urge incontinence had a 50 percent  
14 improvement, 47 percent cured. Again, the 47 percent  
15 who are cured are perhaps the single most important  
16 outcome that we would consider in the urge  
17 incontinence group; half of the patients were cured,  
18 compared to zero percent in the control group.

19 In the urgency frequency group, again, not  
20 quite as impressive results, but also statistically  
21 significant. 15 percent of patients were cured,  
22 meaning they had less than seven episodes per day,  
23 seven voids per day, and 40 percent of them had a  
24 greater than 50 percent improvement.

25 The quality of life outcomes, again, we

00123  
1 have seen these before. For the urge incontinence  
2 group, there were improvements on virtually all of  
3 the measures of quality of life, the SF-36 measures.  
4 Two of these reached statistical significance, the  
5 physical functioning and the general health. For the  
6 urgency frequency group, in contrast to the previous  
7 outcomes, these outcomes were actually much more  
8 impressive for the urgency frequency group, where  
9 there was a greater magnitude of improvement in the  
10 urgency frequency group, sometimes as high as 20 to  
11 30 points on the SF-36 which is a very clinically  
12 significant improvement, and seven of the eight  
13 measures were statistically significant compared to  
14 the control group.

15 Now when we look at the RCT portion of  
16 this study, this basically is a positive study, so we  
17 would next look at, are these results internally  
18 valid, or could these results potentially be  
19 explained by systematic bias, and we would choose  
20 major areas of bias to look at, and to look at each

of these areas and the probability, the potential that these biases are present, and then also the likelihood that these biases, if they're present, might invalidate the results of the study.

As far as selection bias goes, it was a

randomized study, well randomized. There was no indication that the groups were not comparable. A very low problem of selection bias.

Withdrawal bias, I think this is important to talk about, because of the diminishing numbers at each stage of the study. And even though the numbers were diminished, we don't think there was really much likelihood for withdrawal bias because as I said, the actual number of dropouts were actually low, and even though the final number of patients is much lower, we don't feel this is a problem for internal validity. It's more a problem for generalizability of the results. But as far as the internal validity of the RCT portion, we feel withdrawal bias was not a concern.

The main concern for bias was performance bias in this study, and performance bias means the equality of the intensity of treatment between the experimental group and the control group. And in this case of course, the implanted group had a much higher intensity of treatment. And so you can ask, was performance bias a big concern, was the placebo effect a big concern? And there was a high potential for performance bias in this study, and I'll address this in a minute.

I think there are some other aspects of the follow-up that sort of minimize the probability that performance bias explains the results. But there is a potential for performance bias in this study.

Ascertainment bias refers to ascertainment of the outcomes and are the outcomes ascertained in an objective way, and ideally in a way in which there's no knowledge of treatment assignment in ascertaining the outcomes. And we place the potential for this bias at moderate, and this is more

12 a function of the type of outcomes that are used in  
13 incontinence, the fact that these are self reported  
14 outcomes, they're usually patient diaries that are  
15 used to report incontinence. And even the quality of  
16 life data is patient reported data. And of course  
17 the patients know which group they are in so there is  
18 some possibility for ascertainment bias but as I  
19 said, it's more a function of the types of outcomes  
20 that are used in studies of incontinence rather than  
21 a function of the study itself.

22 Now, the next thing we looked at was the  
23 adverse events, adverse effects of the procedure.  
24 And listed here, these have been talked about again,  
25 and are a relatively high rate of adverse effects

00126

1 overall, a total of over 50 percent of the patients  
2 had experienced at least one of these adverse events.  
3 The most common adverse event was pain at the implant  
4 site, and often pain at the implant site was  
5 corrected either by modulation of the stimuli or by  
6 modulation of the device itself. None of these  
7 events that were reported were considered real  
8 serious and most of them as stated previously, were  
9 resolved either with modulation of the impulse or  
10 modulation of the device.

11 There were in the group of urge  
12 incontinence, there were a total of six patients that  
13 required permanent explantation of the device and  
14 following explantation, the adverse effects were  
15 resolved. But it did require taking out the device  
16 in a subset, a small subset of patients.

17 Now the cohort analysis, I bring in here  
18 mainly as a factor to look at in terms of the  
19 randomized control trial in terms of looking at the  
20 durability of the effect and also the possibility  
21 that the difference that we saw in the randomized  
22 trial might be due to performance bias and/or placebo  
23 effect. And as stated previously, the cohort  
24 analysis shows that these effects, this percentage of  
25 patients improved is maintained over at least an 18

00127

1 to 24-month period with really no diminution of  
2 effect. Now if performance bias or placebo effect

3 was operating there, you would expect that there  
4 would be a fall-off in effect. Usually placebo  
5 effects are short lived and will usually either  
6 diminish greatly or disappear by six months, and  
7 certainly by longer periods of time than that. So  
8 this was taken as evidence, corroborating evidence to  
9 the RCT that the effect is durable and also that the  
10 possibility of performance bias explaining the  
11 results is lessened.

12 The therapy evaluation test also gives  
13 further evidence that the effect is truly due to the  
14 device itself. Where the device is turned off and  
15 the number of leaks or voids per day returns roughly  
16 to baseline, and goes back to the previous level  
17 after it's turned on again. This was also used as  
18 evidence that the effect is reversible.

19 Now the comparisons to alternatives, I  
20 think as I mentioned before, is somewhat problematic,  
21 and the comparisons to alternatives, especially for  
22 the urgency frequency syndrome are really lacking,  
23 although I think we can say in the case of urgency  
24 frequency, there's probably less good alternatives  
25 than in the case of urge incontinence. And the

00128  
1 available treatments here, no treatment, surgical  
2 alternatives, or urinary diversion. The results of  
3 the RCT really only allow us direct comparison to the  
4 alternative of no further treatment. And this might  
5 be the appropriate comparison group for those  
6 patients who have gone through all available  
7 alternative, including surgery, but it may not apply  
8 to patients who still have a surgical alternative.

9 As I mentioned, urinary diversion is not  
10 really an acceptable alternative in most cases and we  
11 won't focus on that. So what about the comparison to  
12 surgery? And this would apply primarily to the urge  
13 incontinence patients but also to the urgency  
14 frequency patients, but the data, any data on this  
15 surgical alternative is really in the urge  
16 incontinence patients. So we searched for evidence  
17 of comparison in these patients, and in the AHCPR  
18 guidelines they did a pooled analysis of  
19 enterocystoplasty in patients with urge incontinence.

20 And of 10 studies that they looked at, they estimated  
21 that there was a rate of continence without  
22 catheterization of 38 percent. There was a higher  
23 rate of continence, I think it was more in the 50 to  
24 60 percent range, but these patients may require  
25 intermittent catheterization to manage chronic

00129

1 voiding dysfunction as a result of the surgery  
2 itself. And another thing to mention about this  
3 comparison, it's not directly applicable, because it  
4 would include many patients with neurological origins  
5 of their urge incontinence and really what we're  
6 concerned with are patients with a nonneurological  
7 alternative.

8 We did find one rather large clinical  
9 series of idiopathic detrusor instability, which is  
10 more comparable to the patients with urge  
11 incontinence or approximately 42 patients in which  
12 there was a total of approximately 50 percent of the  
13 patients reported they were either cured or greatly  
14 improved. And this 50 percent could be compared to  
15 the sacral nerve stimulation population, to those who  
16 have a greater than 50 percent improvement, as  
17 probably the most relevant comparison, and there we  
18 have approximately 75 percent of patients who have  
19 improvement, compared to this 50 percent for surgery.

20 So as far as we can make the comparison to  
21 surgery, we can say that it looks like the sacral  
22 nerve stimulation is probably at least as good in  
23 terms of benefit if not better, and certainly, I  
24 think the case is that the surgical alternatives have  
25 higher morbidity, including significant rates of

00130

1 serious morbidity, including death and more serious  
2 morbidity.

3 As far as the relevance to the Medicare  
4 population, this was also discussed previously. The  
5 mean age in the population was 46 years of age in the  
6 urge incontinence and 38 years of age in the urgency  
7 frequency syndrome. We don't really have any data to  
8 say whether or not this is generalizable to the  
9 Medicare population, we don't have any subgroup  
10 analysis or stratification by age. We don't think

there's any evidence that treatment effect differs by age for any of these incontinence treatments, and there is no physiological rationale why elderly patients would respond differently. That's about all we can say about the generalizability to the Medicare population.

So in summary, the strengths of the data are listed here. The strengths of the data are that this is a well done methodologically strong study; it's a multi-center randomized control trial. It's a carefully selected population. The protocol and the outcomes are well described and well reported. I think it deserves reiterating, the prior selection of the patients, meaning the selection by the peripheral nerve evaluation test, is likely to benefit the, or

likely to benefit, likely to maximize the benefit-risk ratio. This is sort of a choose the winner approach, you know, choose who's going to benefit, and I think you could look at this in two ways.

In terms of when you're looking at the magnitude of effect of the study in a scientific sense, it may amplify the magnitude of effect. You might reasonable decide that the denominator of patients that you want to look at would be all patients who are eligible for the device, and then the numerator would be all patients who actually end up benefitting from the device. That would give you a much smaller magnitude of effect. However, the other way to look at it is from a clinical perspective, you're not exposing patients who may not benefit to a potentially invasive procedure where they're not benefitting.

So there's pluses and minuses to it. I think from a scientific perspective, it may somewhat overestimate the magnitude of effect, but from a clinical perspective, it's certainly a good thing.

As far as the benefit, there is positive outcomes and there is a relatively large magnitude of effect on these implanted patients and the numerator

and denominator are relatively large, but in a



2 statistical sense in comparison with the other  
3 studies, there is a large magnitude of effect  
4 compared to other treatments.

5 The results of the cohort analysis and the  
6 therapy evaluation test minimize the possibility that  
7 the results of the RCT are due to bias. And the  
8 adverse effects in the study are not serious ones.  
9 This doesn't rule out the fact that there might be  
10 serious adverse effects, I think that's important to  
11 say. A study of this type, of this duration and  
12 number of patients, is not adequate for fully  
13 determining the true rates of adverse effects and the  
14 true rates of serious adverse effects, and I think it  
15 will be important in the follow-up Medtronic study,  
16 the five-year study with larger number of patients,  
17 to better define what the true rate of adverse  
18 effects is and whether or not there are serious  
19 effects that might occur.

20 The weaknesses of the data, the obvious  
21 weakness is that there's only one study, only one  
22 randomized control study. There are the clinical  
23 series, but there's only one RCT. And as mentioned  
24 previously, there is only a subset of enrolled  
25 patients who achieved benefits. And if you look at

00133

1 the number of patients who actually achieved benefit  
2 to the total number of patients who are eligible, it  
3 is a minority and I think that need to be taken into  
4 account, primarily for the generalizability of the  
5 results.

6 The definition of refractory is not  
7 standardized and all patients did not go through the  
8 exact same prior treatment prior to the procedure.  
9 It's possible that some of the patients may have  
10 benefitted from another type of therapy prior to  
11 getting this, but we don't know that.

12 And then finally, the adverse effect rate  
13 is high. Even though we said it was not serious, it  
14 is high.

15 So in conclusions, we can say that for  
16 patients with refractory urge incontinence or urgency  
17 frequency syndrome, who have a successful peripheral  
18 nerve evaluation test, that sacral nerve stimulation

19 is effective in reducing incontinence or reducing the  
20 frequency of voiding and improving the quality of  
21 life. The magnitude of effect is reasonably large.  
22 We feel this is likely to be more effective than  
23 available alternatives, although this is not  
24 supported by evidence, direct evidence. And it's  
25 also likely to have similar efficacy in the Medicare  
00134

1 population, although again, not supported by direct  
2 evidence. Thank you.

3 DR. GARBER: Thank you, Frank. Les?

4 DR. ZENDLE: Frank, I have two questions,  
5 and I don't know if you can answer both of them.  
6 First is, why wasn't retention addressed like the  
7 other two conditions, urge incontinence and  
8 frequency.

9 DR. LEFEVRE: Well, the retention data was  
10 longer getting through the pipeline than the other  
11 data, and at the time that we had done the  
12 assessment, there was no data on retention published.  
13 We had looked at the unpublished data on retention as  
14 part of our evaluation here, and decided we would  
15 like to see it go through the peer review process  
16 before we would include that in the formal review.

17 DR. ZENDLE: My second question is, I'm  
18 getting the sense that everybody loves this treatment  
19 and I'm wondering, is there any group that doesn't  
20 think this is a worthwhile treatment? I realize you  
21 can't get, necessarily come here and tell us, but in  
22 your looking through the literature and talking to  
23 the clinical experts, did you hear any reluctance by  
24 some to embrace it, and if you did, could you or  
25 maybe some of the people that support the therapy

00135

1 explain maybe their motivation?

2 DR. LEFEVRE: I am probably not the best  
3 one to answer that. I mean, I can probably comment  
4 more on the literature than the experts I've talked  
5 to, which is a subset of experts. I think of the  
6 experts I talked to, most of them were positive. I  
7 think there may have been one out of group of five or  
8 six who had greater reservations in terms of the  
9 technology had not fully evolved, we didn't know

10 really why it worked, we didn't know fully the  
11 mechanisms, and he wanted to see a more complete  
12 understanding of the technology prior to adoption.

13 As far as the evidence in the literature,  
14 I don't think there is really much dissenting view  
15 that I've seen or read.

16 DR. ZENDLE: There are no negative  
17 editorials.

18 THE WITNESS: I don't recall any, no.

19 DR. GARBER: Maybe -- I don't mean this to  
20 be a segue into the committee deliberations, but  
21 Frank, while you're here, there is a question I'm  
22 sure will come up in our panel deliberations and that  
23 is something you touched upon. How do you define  
24 refractory and what's a reasonable definition for the  
25 panel to use based on the data that you have

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1 presented? The slide that you showed that gave the  
2 percentages of different types prior to treatment  
3 showed that virtually everybody received drugs, a  
4 majority had received surgery, and then a minority  
5 behavioral therapy, but a substantial minority. And  
6 there will be a reasonable question that even though  
7 the majority had received surgery, it sounded from  
8 the tenor of all the comments that we heard today  
9 that this would be an alternative to consider before  
10 surgery in people who had failed noninvasive  
11 therapies.

12 How reasonable is it to draw the  
13 conclusion that refractory could be defined as  
14 something like having failed drugs and/or behavioral  
15 therapy? Would that fit with the data that you have  
16 analyzed?

17 DR. LEFEVRE: Well, I think that would fit  
18 with the definition that we had decided upon as  
19 refractory, as what is clinically appropriate for a  
20 definition of refractory, meaning failed both  
21 behavioral and drug therapy. I don't think you can  
22 say it really fits with the data per se, because the  
23 population that we have here, a large number of them  
24 had surgery, but I think that could only probably be  
25 in favor of the data, because the population in the

00137

1 data would be more refractory than the population  
2 that we would consider.

3 Although having already said that, there  
4 is a mix of that, there is a mix because there is  
5 less, you know -- I think it's hard to say, because  
6 the population is really mixed and it's not  
7 standardized as to who got the sacral nerve  
8 stimulation, what they had had previously. I think  
9 clinically it does make sense to make the definition  
10 as having failed behavioral and drug therapy.

11 DR. GARBER: Clinically it does?

12 THE WITNESS: It does make sense I think,  
13 yes.

14 DR. GARBER: Thank you. If there are no  
15 further questions for Frank or for Mitch Burken, we  
16 can proceed to open panel deliberations.

17 DR. TUNIS: I was going to make just one  
18 more comment on the question regarding retention, and  
19 I think it was mostly clarified, but we had been  
20 discussing this with the folks from Medtronic and the  
21 publication I believe is in press now for the  
22 retention data, and it hasn't actually come out yet.  
23 And so for us to provide the panel with the  
24 unpublished data would actually put it in the public  
25 domain, which we obviously couldn't do. So since the

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1 panel couldn't possibly discuss the data on  
2 retention, we decided that we would address that  
3 internally within HCFA, since it should come out in  
4 the time frame that we have available to us before we  
5 have to do our final decision, and we will certainly  
6 take the comments of the panel regarding this other  
7 data into account as we interpret the retention data.

8 DR. HOLTGREWE: Would a motion be  
9 appropriate at this juncture?

10 DR. GARBER: It depends on what the motion  
11 is.

12 DR. HOLTGREWE: I move that the committee  
13 recognize there is adequate evidence to draw  
14 conclusions about the effectiveness of sacral nerve  
15 stimulation in the Medicare population for two  
16 indications, refractory urinary urge incontinence,  
17 and refractory urge frequency syndrome.

18 DR. GARBER: Okay. Is there a second to  
19 that motion?

20 DR. SIGSBEE: Second.

21 DR. GARBER: Discussion? Yes, Adrian.

22 DR. OLECK: I just wonder whether there's  
23 any concern from the other panel members about this  
24 issue of the neurological patients. I still,  
25 neurological conditions seem to be underlying cause

00139  
1 for some of these people with incontinence, and this  
2 is a treatment that is aimed at neuromodulation, and  
3 I guess I'm a little uncomfortable with the fact that  
4 those people were specifically excluded from the  
5 study and yet the recommendations we're proposing  
6 don't address that at all. Is that a concern to  
7 anyone else?

8 DR. HOLTGREWE: The problem you have when  
9 you include neurological disorders is it is such a  
10 mixed bag. You can't even say that multiple  
11 sclerosis patients all act the same; they're all  
12 different. And I think that it was appropriate in  
13 the studies that were constructed here to exclude  
14 these people, because it would be a confounding  
15 factor to an enormous degree. Now this doesn't mean  
16 that this might not be an acceptable technology, but  
17 I think it awaits further study.

18 DR. GARBER: Adrian, as I understand the  
19 way that the questions were formulated, they adhere  
20 closely, perhaps not perfectly, to the way the  
21 studies were designed, so that the indications  
22 closely correspond to the randomized trials, and I  
23 think that's perhaps one of the reasons people don't  
24 feel uncomfortable about that issue. Les?

25 DR. ZENDLE: I thought maybe I would just

00140  
1 address two of the follow-up points that go along  
2 with that question, because I think it probably needs  
3 to be reiterated, and it came up in both the  
4 testimony and the assessment, and that's that  
5 although it is reasonable to say that the results are  
6 applicable to the Medicare population, that's not  
7 from direct evidence, it's probably from indirect  
8 evidence. And again, that doesn't in any way make me

9 reluctant to approve this, but I just think it should  
10 be noted.

11 And secondly, although this should be  
12 generalizable beyond the research setting, many  
13 people stressed the importance of training and  
14 adequate proctoring and all that, and I think the  
15 fact that Medtronic has such a good program is to be  
16 commended, but I also think we ought to state that  
17 there is a learning curve and that, I don't know how  
18 to state some concern, that only those who are  
19 appropriately trained do this procedure.

20 DR. GARBER: That's something you can do  
21 internally at HCFA?

22 MS. CONRAD: Yes.

23 DR. GARBER: In fact, you might want to  
24 take your point to say this is how you address  
25 whether this generalizes beyond the research setting,

00141  
1 since they have instituted a training program, so  
2 under those conditions, that's how it generalizes.

3 DR. ZENDLE: Yes. And I don't think it  
4 needs to be in the motion but I wanted it to be in  
5 the discussion, that we agree that it should be part  
6 of, or that I agree anyway, that it should be part of  
7 the training program and that helps me feel  
8 comfortable that there's enough evidence that this is  
9 worthwhile.

10 DR. SIGSBEE: Just a point of  
11 clarification, I at least had understood that under  
12 the FDA approval process, this device could be sold  
13 only to physicians who met the criteria of going  
14 through the training program, so there is that  
15 barrier already in place. And so, somebody can't  
16 just decide that they're going to start implanting.

17 DR. TUNIS: Just also to further explore  
18 that, if any of the folk from Medtronic could comment  
19 on this. It would be helpful for us to understand a  
20 little bit more about how much of the training is  
21 required to get the typical practitioner up to speed  
22 in terms of being able to do not only the  
23 implantation, but the test procedures, et cetera? Is  
24 there any kind of comments on that in terms of the  
25 proctoring program?

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1 DR. GARBER: Sorry, Connie. We have to  
2 take roll call.

3 MS. CONRAD: Excuse me. For today's panel  
4 meeting, voting members present are Michael Maves,  
5 Kenneth Brin, Logan Holtgrewe, Angus McBryde, Bruce  
6 Sigsbee, and Les Zendle. A quorum is present. No  
7 one has been recused because of conflicts of  
8 interest. Thank you.

9 DR. GARBER: Sorry. You can go ahead now.

10 MS. ARONSON: The question is, what's  
11 really involved and how can we -- can you restate the  
12 question one more time for me?

13 DR. TUNIS: I'm trying to get a sense of  
14 how in any way we would be able to understand what  
15 sort of adequate training to get people who are  
16 learning this procedure up to the point where they  
17 are competent by some measure.

18 MS. ARONSON: Right. Well as we  
19 mentioned, the process is first the day and a half  
20 didactic course, which includes a cadaver work shop.  
21 Then the proctorship on the first two stimulations,  
22 and another proctorship on the first two implants.  
23 Following each one of those steps, it's reviewed by  
24 both proctor and the person being proctored and at  
25 that upon, if it's felt by either party that

00143

1 additional training may be required, or if the  
2 proctor would get in and say for example, I really  
3 didn't feel comfortable that this physician was  
4 comfortable doing the therapy, as I mentioned before,  
5 we have established sites across the country of our  
6 experienced implanters, where this person can then go  
7 to one of the on-site locations and get additional  
8 training. So we really do take it to all the steps  
9 to make sure that both parties feel as though we have  
10 a proficient test stimulator and implanting  
11 physician.

12 DR. TUNIS: Just, I've learned for the  
13 first time that there is an FDA requirement that this  
14 training be in place.

15 MS. ARONSON: That's correct. When we  
16 received the initial FDA approval in September of

17 1997, the FDA did mandate that as a condition of  
18 approval, we would establish a training program. So  
19 this is the training program that we discussed and  
20 agreed upon with the FDA.

21 DR. TUNIS: Okay. So the FDA actually  
22 reviewed the contents of the training program?

23 MS. ARONSON: That's correct.

24 SPEAKER: I took the course in November,  
25 Dr. Siegel came and proctored me in February, and we

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1 did the first implants in March. The rep from the  
2 company still comes for all our test implants, he  
3 still comes for all my surgical implants, because I  
4 still feel like I need that feedback. It's not that  
5 he's showing me how to do anything, but he's there in  
6 case I have questions. If he doesn't know, he calls  
7 the company or Dr. Siegel, and he will actually be  
8 there until I tell him I don't want him anymore.

9 The other thing is not just the surgical  
10 implant of it, it's also doing the fine tuning when  
11 the patients come in to get activated, and it's not  
12 unusual to need to fine tune them several times in  
13 the first six months to 12 months. And again, the  
14 sales rep comes back for all the activations. My  
15 nurse, they went to a course to learn how to do the  
16 activations, but a lot of it is not just you push  
17 this button and this button, but it's a lot of  
18 clinical playing around and again, there are very  
19 supportive.

20 DR. GARBER: Do any of the panelists want  
21 to address this issue about how we define refractory,  
22 or would you rather leave the language just  
23 refractory, without a definition? I think HCFA would  
24 probably -- would you like somewhat more guidance  
25 than just refractory or not, from the panel?

00145

1 DR. ZENDLE: Really, the question is do  
2 you include surgical in refractory, and I think  
3 people want to avoid, one, many people want to avoid  
4 it, and two, it's an alternative, and it appears this  
5 has better outcomes than surgical, so why would we  
6 want to include that as a definition?

7 DR. GARBER: Right. You could define



8 refractory without requiring prior surgery to be part  
9 of refractory, if that's the way you feel.

10 DR. ZENDLE: Do we really need to though?

11 DR. HOLTGREWE: The surgical procedures  
12 that are used here are, number one, virtually  
13 irreversible and carry with them substantial risks  
14 far in excess of what we have looked at here this  
15 morning in terms of sacral nerve stimulation, so I  
16 think the algorithm would be failure of medical  
17 management and behavioral therapy, and then you go to  
18 SNS rather than going to surgery. Surgery was used  
19 because there was no other alternative at that time.

20 DR. GARBER: Bruce?

21 DR. SIGSBEE: It's been said.

22 DR. GARBER: I think we're all in  
23 agreement about the circumstances in which it should  
24 be used. The question is, do you want to have  
25 language to the effect that refractory means failure

00146

1 of, you might call it conservative measures, i.e.,  
2 drugs and/or behavioral therapy?

3 DR. ZENDLE: What would the purpose of  
4 that be? Are we afraid that somehow HCFA is going to  
5 require someone to have surgical before they get  
6 this?

7 DR. GARBER: Well, that's certainly -- if  
8 you go straight from the studies, where you have the  
9 majority of people getting surgery, that is an  
10 inference that's possible to draw. So if you felt  
11 strongly that you didn't want to require surgery, you  
12 might want to define refractory.

13 DR. ZENDLE: Again, I don't think we are  
14 addressing coverage here, so I don't see a need to be  
15 really stating that.

16 DR. GARBER: I'm just trying to make sure  
17 we have this issue covered, so if you want to say  
18 anything, it's the sense of the panel that you don't  
19 want to define refractory?

20 DR. MCBRYDE: It seems to me that if you  
21 do, you would have to include a time limitation too,  
22 that ought to be one of the requirements, and then  
23 define surgery, because all of them virtually I'm  
24 sure have had cystoscopy and some other procedural

25 stuff, so are we talking about those major surgeries.  
00147

1 DR. GARBER: Okay. So, the motion on the  
2 floor is the language as stated in the questions  
3 posed to the panel and the answer to the question --  
4 Logan, you were the one who made the motion?

5 Dr. HOLTGREWE: I made the motion.

6 DR. GARBER: And it was to answer it yes,  
7 correct?

8 DR. HOLTGREWE: Correct.

9 DR. GARBER: Any further discussion?

10 Dr. MCBRYDE: While we're waiting, can I  
11 ask two small points related to Medicare population?  
12 First of all, did any of the Medicare population in  
13 any of the studies get dry, in other words, they got  
14 a total hundred percent cure? I remember some of  
15 them did in the younger population. Did they,  
16 Dr. Siegel?

17 DR. SIEGEL: Yes.

18 DR. MCBRYDE: Okay. And secondly, were  
19 any of the patients involved, even though initially  
20 they weren't suspect for any neurological disease,  
21 did any of them turn out or have they turned out in  
22 any of the studies to have some M.S. Or some sort of  
23 neurological problem?

24 DR. SIEGEL: I am not aware of any.

25 DR. GARBER: Are there any members of the  
00148

1 public who have not spoken, or who have spoken and  
2 would like to speak now?

3 MS. OLESON: I would just like to address  
4 the question on defining what refractory means, and  
5 if -- the subjects in the study were indeed  
6 refractory to all forms of therapy, including surgery  
7 in 58 percent of the subjects. We also did follow  
8 after implant the use of concomitant therapies,  
9 including drugs, interventions and surgeries. And  
10 what we had seen with long-term follow-up past 24  
11 months, the use of non-Inter-stim related surgeries  
12 dropped from a baseline of 58 percent of patients  
13 down to less than 3 percent through several years of  
14 follow-up, so that might help you to address the  
15 issue of defining refractory.

16 DR. GARBER: Thank you, although we have  
17 already decided not to define it, but HCFA should  
18 take that into account. Yes.

19 DR. BENSON: I would also like to address  
20 the question about surgery as a prerequisite. These  
21 patients have a combination of symptoms, stress  
22 incontinence and urge incontinence. Most of the  
23 surgical procedures were stress incontinence  
24 procedures, which are sort of done as the last resort  
25 in patients before you had other modalities of

00149  
1 therapy. Nothing else has worked, so I'll try my  
2 stress incontinence procedure. So requiring surgery  
3 to be failed in this group would be self defeating,  
4 so it should not be a prerequisite before they go to  
5 this kind of therapy. The only real surgery for the  
6 urge incontinence group are denervation procedures or  
7 bladder augmentation procedures or shunting.

8 DR. GARBER: Thank you.

9 DR. TUNIS: Maybe this is a question for  
10 Dr. Siegal or other folks involved in the trial, but  
11 when Dr. Lefevre was reviewing some of the  
12 information about the prior therapies that patients  
13 had had, it looked like something on the order of 50  
14 percent overall for the two indications had had prior  
15 behavioral therapy. And I guess the question to you  
16 is given the relatively high rate of adverse events,  
17 why wasn't the behavioral therapy sort of a required  
18 prior intervention.

19 DR. SIEGEL: This is a factor of the fact  
20 that the study took place in 22 centers, in several  
21 different countries, and the standards of therapy  
22 available to the patients differed greatly. For  
23 example in our center, 100 percent of the patients  
24 enrolled had conservative therapy including  
25 biofeedback and other interventions. And in some

00150  
1 centers where this was not routinely offered, maybe  
2 none of the patients did. So I think the problem has  
3 to do with the number of study centers throughout the  
4 world that were enrolled, and I would continue to  
5 encourage my colleagues here in the United States at  
6 least to follow the standard that was discussed

7 today, which is some sort of trial of behavioral  
8 therapies and drug therapies before consideration of  
9 sacral nerve stimulation.

10 DR. TUNIS: So maybe then, and this is  
11 more in the form of badgering the panel, but they  
12 don't have to respond if they don't want to, but kind  
13 of along these same lines is that one way clearly we  
14 will be internally thinking about this whole notion  
15 of refractory therapy is whether to approach this as  
16 patient should have failed adequate behavioral  
17 therapy and drug therapy prior to going to sacral  
18 nerve stimulation, the logic of that being this  
19 relatively high rate of adverse events. That's what  
20 I would throw on the table. I'd just like to get  
21 some feedback from either the panel or the audience  
22 on the wisdom or lack of wisdom of that, given that  
23 we're going to have to talk about it internally.

24 DR. BENSON: When you say and there, there  
25 are some patients who cannot use the drug therapy

00151  
1 where it's contraindicated.

2 DR. ZENDLE: I think it's common sense to  
3 say that they have to fail those two therapies, but I  
4 include failed therapy as a patient that is not able  
5 to take it or whatever, I include that as a failure.  
6 So I don't think we need to go beyond that, just  
7 because it's so common sense, but if you want us to,  
8 we could.

9 DR. GARBER: Yes, Mike.

10 DR. MAVES: You know, Sean, I think your  
11 point is a good one and it actually is something that  
12 I sat and wrestled with a little bit. I think the  
13 question is how to select the patients that receive  
14 this treatment. I think the refractory language will  
15 give the Agency guidance on that with the sense that  
16 the panel feels that ought to be, and I think, you  
17 know, how that actually gets implemented into a  
18 coverage decision is clearly in the purview of you  
19 and the rest of the folks at HCFA.

20 So, those are two things that I sort of  
21 thought a little bit about, but I think again, the  
22 sort of coverage itself is not our purview, and I  
23 think the refractory language helps me at least to

24 say, yes, I think there needs to be some sort of a  
25 selection that goes on in these patients, I have  
00152  
1 several questions about that, but I'm satisfied that  
2 this is not something that gets offered to patients a  
3 priori without having some, it sounds like everybody  
4 had something done in some form, and for any variety  
5 of reasons, they may or may not be able to tolerate  
6 it, and I think the refractory language captures that  
7 for me.

8 DR. GARBER: Bruce?

9 DR. SIGSBEE: Plus, I think that we have  
10 to avoid trying to micromanage clinical practice. If  
11 the clinician has an algorithm and decision process,  
12 and new information may come forward next year that  
13 modifies the sequence of how the procedures are  
14 offered the patients, and I'm not sure it's worth  
15 trying to codify regulations in this specific  
16 sequence this morning.

17 DR. TUNIS: Okay. I think just to further  
18 express at least the concern that I'm laying on the  
19 table is that I'm imagining that should coverage be  
20 provided for this procedure, that the number of  
21 practitioners offering it will be much higher,  
22 whether or not Medtronic has the infrastructure to  
23 provide the same level of attention and training to a  
24 much broader group of practitioners is unknown, and  
25 so the adverse event rates that are reported in these

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1 trials are likely to go up substantially.

2 And so, you know, I don't think we spent a  
3 lot of time talking about the adverse events, but  
4 that's the issue and why I'm kind of pressing on this  
5 issue.

6 DR. GARBER: Well, I think you have the  
7 clear understanding from the panel that first of all,  
8 this was done in a multi-institutional trial, so it  
9 is not all of one site, one person operating or  
10 anything like that. And I think if I'm correctly  
11 reporting the sense of the panel, the assumption is  
12 that this would only, that our conclusion about  
13 adequacy and presumably effectiveness, presumes that  
14 they get training similar to the training of the

15 physicians participating in the trials. And I don't  
16 know how reassured you should feel by the fact that  
17 that's a condition for FDA approval, but in fact that  
18 is what our discussion is predicated on, that they  
19 will get comparable training. So, that's actually  
20 better than is typical for surgical procedures. Ken?

21 DR. BRIN: Just to address that very  
22 directly, in my area, particularly in interventional  
23 cardiology, most new technologies that come out,  
24 there is a very formal training period. The formal  
25 training period is mandated in essence by the FDA

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1 through how they approve that device or that  
2 technique, but it is also mandate by each  
3 individual's hospital's credentialing committee,  
4 which requires that. And I say that both in terms of  
5 trying to reassure HCFA that these mechanisms are set  
6 up, but also with the hope that the HCFA final ruling  
7 does not address, other than to mention appropriate  
8 training, because if in fact we have to as  
9 practitioners provide evidence to our local  
10 intermediary that we have gone through the training,  
11 this is going to add yet another level of  
12 administrative difficulty that is already being met  
13 by at least two other levels.

14 DR. GARBER: Okay.

15 DR. MCBRYDE: I have one other thought.  
16 It is worth thinking about that in a little more  
17 depth, because much of your information about the  
18 initial diagnoses, not the Steves of the world, but  
19 in urology, there are a number of people I'm sure  
20 that have psychological problems that have this type  
21 of thing, it's all subjective, most of your outcome  
22 as well as your income, if you will, is subjective.  
23 So it is important to step back even one step  
24 further. You can always document treatment, but you  
25 can't always document, is this really the problem, so

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1 the diagnosis itself becomes really important too,  
2 not to have it mixed on the front end even one step  
3 back from the treatment documentation.

4 DR. GARBER: Okay. Anybody else from the  
5 public want to speak. If not, does anybody from the

6 panel want to raise further discussion? If not,  
7 we're ready to take a vote.

8 The motion on the floor is to answer yes  
9 to question one about adequacy of evidence. All  
10 those in favor?

11 Unanimous.

12 I'm going to ask you to quickly, we don't  
13 need to spend a lot of time, go through the reasons  
14 for your vote, preferably addressing the consistency  
15 of the results, the applicability to the Medicare  
16 population, generalizability beyond the research  
17 setting. Start with --

18 DR. ZENDLE: I thought we did this  
19 already.

20 DR. GARBER: It's implicit in your  
21 comments, but not everybody spoke on all of these  
22 points, and you can say you agree with the person  
23 before you. So Les, you can start off.

24 DR. ZENDLE: I think I already stated my  
25 opinion and the reasons why I support it.

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1 DR. GARBER: Okay, Ken?

2 DR. BRIN: I already said my bit  
3 previously. Let me address, consistency when there  
4 is one study is relatively irrelevant.  
5 Applicability, I think we have discussed that  
6 already. It would be nice to have more data and I  
7 presume with time we'll get more data, but we can  
8 only use what our experts have otherwise mentioned  
9 which is, it is highly likely, and then watch the  
10 outcomes here.

11 As far as generalizability, I think that  
12 many of the settings in which it has been used are  
13 what one would call routine clinical settings, so I  
14 think it is generalizable.

15 DR. GARBER: Thanks. Angus?

16 DR. MCBRYDE: My vote is yes. I do think  
17 there are, and I don't know enough about the  
18 potential for abuse, and it's not our purview in this  
19 committee to talk about CPT codes and how many would  
20 be used, and what the accelerated usage of the  
21 implant would be, but it's something to keep in mind.  
22 It's efficacious in my opinion.

23 DR. GARBER: Logan?  
24 DR. HOLTGREWE: I felt that the two  
25 randomized prospective trials that were presented  
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1 were rather compelling, and I feel that they  
2 demonstrate without question that this is a valuable  
3 technology, in the absence of anything else as good.  
4 DR. GARBER: Thank you. Mike?  
5 DR. MAVES: I will echo Dr. Brin's  
6 comments.  
7 DR. GARBER: Okay, ditto. Bruce?  
8 DR. SIGSBEE: As a neurologist, I think I  
9 would like to comment a little bit about the concern  
10 with neurological procedures, particularly M.S. I  
11 would probably have done the same thing in setting up  
12 the research protocol to exclude particularly  
13 patients with M.S. The underlying physiology of this  
14 methodology is not known, there is an important  
15 afferent arc, M.S. Patients have lesions spread  
16 throughout the nervous system, and a failure in that  
17 patient, it's not known whether it would be due to a  
18 failure of the technique, or was it because there is  
19 in that particular patient interference with the  
20 appropriate arc. We're talking about a contin level  
21 vectoration center, and obviously a lot of lesions  
22 could exist between the stimulation site. So I think  
23 that it was very appropriate to have as clean a study  
24 population with as few variables as possible to  
25 demonstrate to try to demonstrate whether the  
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1 technique works or not. But also in my view, I think  
2 it is probably entirely generalizable to neurologic  
3 patients and their problems and we will get more  
4 data.  
5 DR. GARBER: Okay, thank you. Is the  
6 panel ready to tackle the second question? Les?  
7 Dr. ZENDLE: Yeah. I'd like to move that  
8 we answer the second question as fitting the category  
9 of more effective, and I will state why after  
10 somebody seconds.  
11 DR. GARBER: Is there a second to that  
12 motion?  
13 DR. McBRYDE: Second.



14 DR. GARBER: Okay.

15 DR. ZENDLE: I think, as was discussed  
16 when we were talking about the first motion, and as  
17 the case was presented, there are some problems with  
18 the results, and I think what it leads me to believe  
19 is that I'm not so sure -- I don't think it's a small  
20 effect, I don't think it's a large effect, it's  
21 somewhere in between, and I think to have to say  
22 something is a breakthrough technology is maybe just  
23 the semantics of the word. I don't know that there's  
24 enough evidence to support that. But I also don't  
25 think it's relevant to the information that HCFA

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1 needs, and we have all stated that we are going to  
2 have to see how the results keep coming in,  
3 especially in regards to the Medicare population. So  
4 I have no trouble supporting more effective at this  
5 point.

6 Dr. GARBER: Logan?

7 DR. HOLTGREWE: I would concur. I think  
8 that part of the definition we've been given by HCFA  
9 that the outcome is so large that the intervention  
10 becomes a quote, standard of care, closed quote, and  
11 I'm not convinced at this juncture that that this is  
12 quote, standard of care, closed quote, where you  
13 really have to do it or you're guilty of malpractice,  
14 which is the definition of standard of care, so I  
15 think more effective is the proper category.

16 DR. GARBER: Further discussion? So the  
17 motion on the floor is to assign it Category 2, more  
18 effective.

19 All those that in favor?

20 Unanimous.

21 Well, I think that ends our business.

22 Connie?

23 MS. CONRAD: To conclude today's panel  
24 meeting, I would like to announce that the Executive  
25 Committee is scheduled to meet November 7th, here in

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1 the Convention Center. And I would like to thank all  
2 the panelists and participants, and could I have a  
3 motion that the meeting be adjourned?

4 DR. GARBER: Actually, before we have that

5 motion, let me also thank the people who spoke on  
6 behalf of the public. I think you could see that  
7 there were a lot of questions for you, the  
8 information was very helpful to the panel in its  
9 deliberations.

10 I will now entertain a motion for  
11 adjournment.

12 DR. HOLTGREWE: So moved.

13 DR. SIGSBEE: Second.

14 DR. GARBER: All in favor?

15 (The meeting adjourned at 11:57 a.m.)  
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